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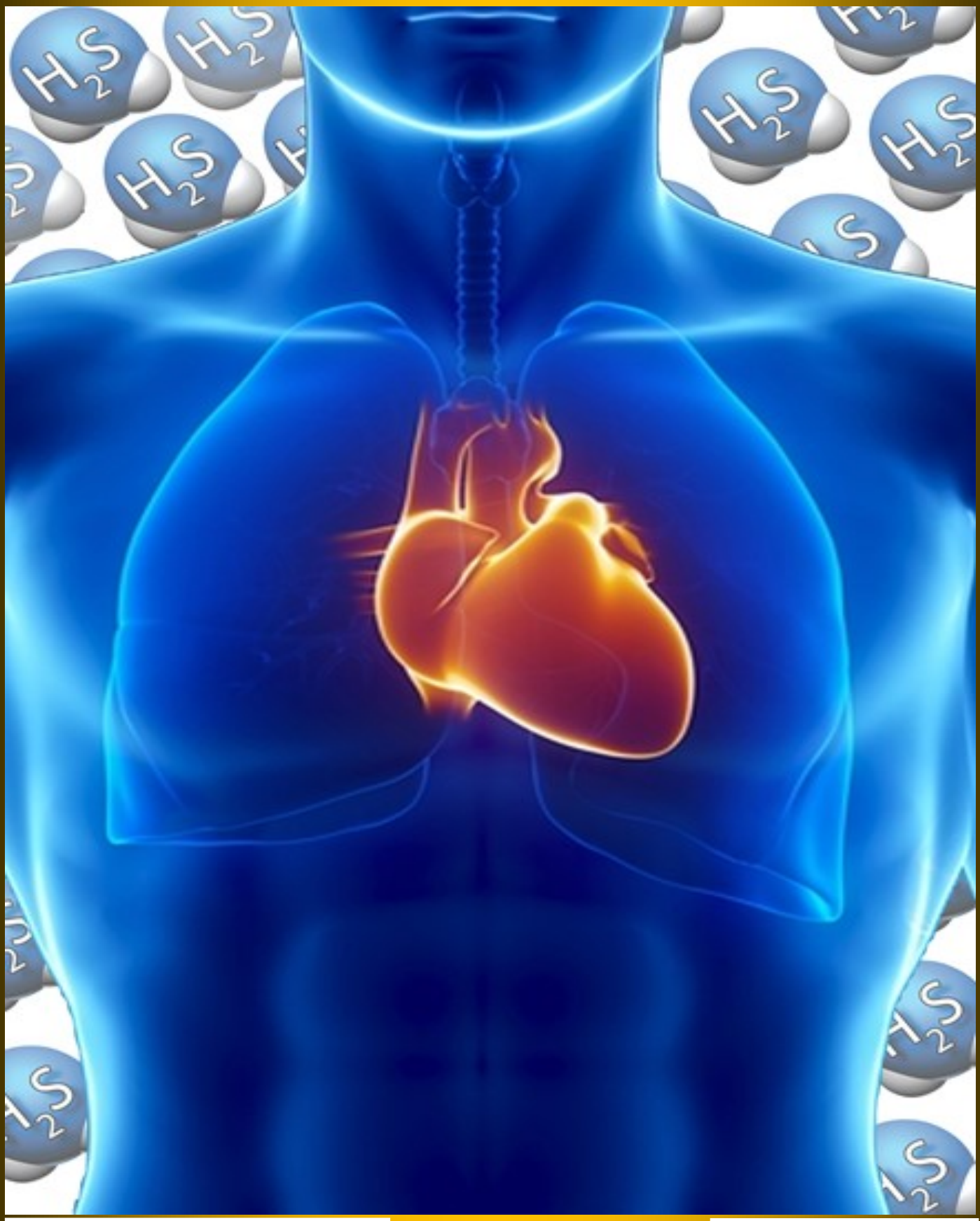
DRUG INFORMATION FOR THE HEALTH PROFESSIONAL



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Role of hydrogen sulfide in hypertension and cardiovascular diseases

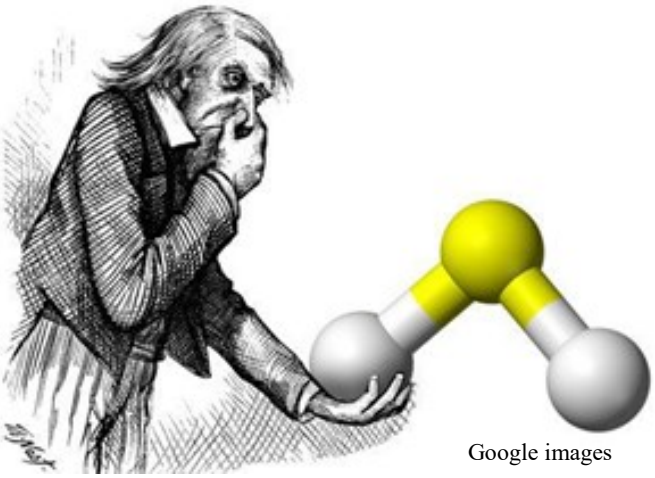
Hydrogen sulfide (H_2S) is a colourless gas with characteristic rotten egg smell with toxicity ranging from eye irritation to coma, leading to death. The olfactory response is the first defense mechanism and it can be lost at concentrations of 100-150 ppm, indicating a real danger. H_2S can be synthesized endogenously. The enzymatic pathway is mediated by cystathionine B-synthase (CBS), cystathionine γ-lyase (CSE) and cysteine-aminotransferase (CAT) in conjugation with mercaptopyruvate-sulphurtransferase (3-MST). H_2S can be metabolised by several mechanisms, including methylation and oxidation. It affects the central nervous system through modulation of glutamate, GABA, norepinephrine and serotonin. H_2S also affects the endocrine system and inhibits insulin release. H_2S has both pro-inflammatory and anti-inflammatory effects. In the cardiovascular system, it is claimed to have negative chronotropic and inotropic effects. It also induces vasorelaxation and inhibits vascular smooth muscle cell proliferation. Moreover, H_2S has a stimulatory effect on vascular endothelial cells proliferation. Due to these effects, H_2S has been suggested to play a role in the pathophysiology of cardiovascular diseases such as hypertension, atherosclerosis, myocardial ischemia, as well as heart failure, and therefore it is an attractive target for management of cardiovascular diseases.

Introduction

Hydrogen sulfide (H_2S) is a colorless flammable gas ofmolecular weight 34 and vapour density of 1.19, making it heavier than air. It has a characteristic rotten egg smell. Its half-life in normal air is around 12h, extended to 37 h in very cold and dry air. It is a weak acid with a dissociation constant of 6.76 at 37°C. It can dissociate into hydrogen ion and hydrosulfide anion, which may dissociate into another hydrogen ion and sulfide anion ($H_2S \leftrightarrow HS^- + H^+$). H_2S is a highly lipophilic molecule so easily penetrates the lipid bilayer of the cell[1].

Our olfactory response is the first defense mechanism against H_2S with a low sensing threshold. of 0.1 to 1 ppm. Strong odor of H_2S can be tolerated, but at 27 ppm eye irritations occur. In acute H_2S exposure (up to 50-100 ppm), toxicities include neurological symptoms of dizziness and headaches, vigor skin symptoms such as itching, dryness and redness and general deficits including nausea, gastrointestinal tract upsets and loss of appetite. It also leads to behavioral changes including anger and depression.

H_2S toxicity can cause respiratory symptoms such as apnea, non-cardiogenic pulmonary edema, cough and cyanosis, and cardiovascular abnormalities including irregular heartbeats or hypotension[1]. At a concentration of 100-150 ppm, the olfactory nerves will be paralysed[2]. At 320-530 ppm there is pulmonary edema and possibly death, while 530-1000 ppm will lead to a strong stimulation of the CNS and rapid breathing followed by sudden loss of breath, and death.



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Synthesis of H_2S occurs endogenously through the reverse trans-sulfuration pathway. The source of H_2S in the body is methionine and cysteine. In the presence of L-cysteine and homocysteine, two pyridoxal 5'-phosphate (PLP), CBS and CSE catalyse the production of H_2S[3].

CBS catalyses conversion of methionine to cysteine and the condensation of cysteine and homocysteine to give cystathionine and H_2S. Even with six-fold higher concentration of cysteine, serine inhibits H_2S formation from cysteine and 2-mercaptorthanol only by 50%[4]. This confirms that L-serine is a better substrate than cysteine with homocysteine being the co-substrate.

CSE catalyses the second step of reverse trans-sulfuration,

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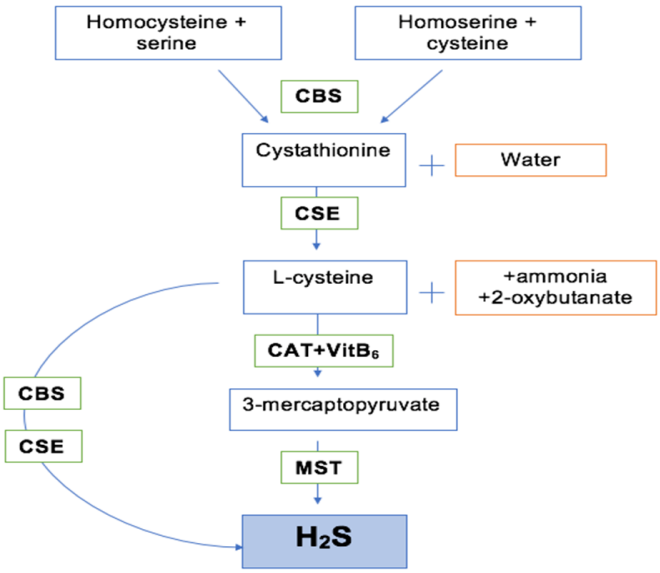

Fig 1. Synthesis of H_2S.

which involves the cleavage of C-γ-S bond of cystathionine to yield L-cysteine and 2-oxobutanoate and ammonia[1]. CSE forms H_2S, ammonia and pyruvate, using L-cysteine as a substrate. CSE is also involved in conversion of L-homoserine to water, ammonia and 2-oxobutanoate. Moreover, it catalyses L-cysteine conversion to thiocysteine, pyruvate and ammonia[1].

MST and CAT work together in the presence of 2-oxoglutarate and PLP to produce H_2S. CAT converts cysteine to 3-mercaptopyrovate, using PLP as a cofactor. MST then transfers the sulfur, which presents in the sulfane group of 3-mercaptopyrovate, to another sulfur acceptor, using zinc as a cofactor. Rhodanese, a mitochondrial protein also known as thiosulfate sulfurtransferase, is another biological sulfur-carrying enzyme in our bodies; however, its biological and physiological importance is not fully determined[3]. The enzymatic pathway of H_2S synthesis is summarised in Fig 1.

The non-enzymatic reduction of elemental sulfur, using reducing equivalents obtained from oxidation of glucose in erythrocytes, is a minor source of endogenous H_2S. Through the non-enzymatic oxidation, sulfides produce thiosulfate which is then converted to sulfite in the liver, kidney or brain tissue by thiosulfate reductase, or by thiosulfate sulfurtransferase in the liver. Moreover, H_2S can be released from thiosulfate and persulfate[1].

Two molecules of H_2S in mitochondria are oxidized to one molecule of thiosulfate, which is then converted by sulfide detoxifying enzymes into sulfate that is renally excreted as free or conjugated forms[5]. Rhodanese, a sulfide detoxifying enzyme, has two isoforms: thiosulfate cyanide sulfurtransferase (TST) and MST. TST can detoxify H_2S and thiosulfates, but MST cannot[1].

H_2S can also be methylated by thiol S-methyltransferase (TSMT) into methanethiol, a colourless gas that also smells like rotten cabbage. In a slower rate, methanethiol is further methylated by the same enzyme into dimethyl sulfate, a non-toxic compound[1]. Moreover, the lung can also participate in the excretion of H_2S, if it is generated in high concentration; in hemorrhagic conditions, septic shock or pancreatitis[5].

Physiological effects of H_2S in the cardiovascular system

Chronotropic and inotropic effects of H_2S

H_2S is claimed to have a negative chronotropic due to inhibition of pacemaker cells in sinoatrial (SA) nodes. Glibenclamide, a potassium channel inhibitor, but not caesium chloride (CsCl) inhibits this negative chronotropic effect, suggesting that the effect of H_2S is due to the opening of K_{ATP} rather than I_f channels[1].

On the other hand, H_2S has a negative inotropic effect and reduction of central venous pressure in irreversible ischemic rat hearts. Although another study showed the same effect on mice receiving 1 mg/kg NaHS, not all studies supported the negative inotropic effect of H_2S on the heart. A study on isolated rat ventricular myocytes showed no effect of NaHS (50 or 100 mM) on contraction of myocytes[1].

Vasorelaxant effect of H_2S

H_2S-induces relaxation in aorta, portal vein, mesenteric artery, cerebral arteries, and vas deferens from different species such as rats, mice, cows, guinea pigs, sheep and human[1]. H_2S-mediated dose dependent relaxation of rat aorta pre-contracted by phenylephrine, was reported to act through opening K_{ATP} channels[6]. This relaxation response of H_2S is observed in large vessels, but it shows more effect on small resistance rather than large conduit arteries[7]. The mechanism of H_2S-induced vaso-relaxation involves mostly endothelium-independent and to a lesser extent endothelium-dependent mechanisms[8]. Endothelium-independent effects of H_2S include its effect on K_{ATP} channels, voltage-gated potassium (K_v) channels, calcium-activated potassium (K_{Ca}) channels and endoplasmic reticulum/sarcoplasmic reticulum (ER/SR) calcium

release channel. It also includes the changes in intracellular pH and metabolic inhibition.

The major molecular target of H_2S for its vasorelaxant effect is K_{ATP} channels on vascular smooth muscles. The induced hyperpolarisation closes voltage gated calcium channels, leading to a reduction in intracellular Ca^{+2}, thus resulting in smooth muscle relaxation[9]. Since K^+ current that is generated by inward rectifier potassium channel (K_{ir}) is insensitive to H_2S, sulfonylurea receptor (SUR) subunits are the sites of modulation. The activation of K_{ATP} channels by H_2S is independent of the intracellular ATP levels. H_2S opens K_{ATP} channels by interacting with Cys6 and Cys26 residues on the extracellular N-terminals of rat vascular SUR1 subunit of K_{ATP} channels and modifies it through S-sulfhydration, thus opening the channel[9]. The vaso-relaxation is not only exerted through K_{ATP} channel opening, as it is reported that glibenclamide can only partially prevent H_2S-induced vaso-relaxation or produce no effect in some blood vessels[10].

Moreover, H_2S induces vaso-relaxation via activation of K_v channels through the ADRF-K_v pathway, in which peri-adventitial adipose tissue (PAT) releases H_2S, an adipocyte-derived relaxing factor (ADRF), then H_2S will activate $K_v7.x$ channels in vascular smooth muscle[8]. It acts by activating K_v7 channels at around -69 mV and keeping the resting membrane voltage far away from the threshold for activating the voltage-gated calcium channels, which is around -40 mV, which will, in turn, prevent vasoconstriction[10].

Additionally, H_2S exerts its vasorelaxant effect via K_{Ca} channels. Large conductance calcium-activated potassium (BK_{Ca}) channels reduce the contractile response in vascular smooth muscles following an increase in Ca^{2+} levels. Calcium sparks a temporarily limited local increase in intracellular Ca^{2+} when ryanodine receptors (RyRs) open in sarcoplasmic reticulum membrane. There is an increase in local concentration of Ca^{2+} in sub-sarcolemmal space which increases the opening probability of BK_{Ca} channels[11]. Then BK_{Ca} channels hyperpolarise the membrane and reduce the opening frequency of voltage-gated calcium channels and there is reduction in global intracellular Ca^2. In rat mesenteric arteries, CSE is inhibited by B-cyano-L-alanine; this reduces Ca^{2+} spark frequency, however, adding NaHS increases Ca^{2+} spark frequency in the endothelium of the artery. This study confirms that H_2S induces Ca^{2+} spark, leading to its vasorelaxant effect [12]. Some studies showed that the effect of H_2S on BK_{Ca} channels is dose-dependent[13].

H_2S also works on ER/SR calcium release channels to act as a vasorelaxant. Ryanodine receptors participate in Ca^{2+} mobilisation in smooth muscle[14]. H_2S donors increase Ca^{2+} spark frequency in vascular smooth muscle cells of piglet cerebral, while in vascular smooth muscle (VSM) of rat mesenteric artery, H_2S donors decrease intracellular Ca^{2+} [12,15].

Another mechanism through which H_2S acts as a vasorelaxant is by inducing pH changes. Vasorelaxation is caused by intracellular acidification while vasoconstriction is caused by alkalisation. Intracellular pH in VSM cells is maintained by buffering systems and ionic exchangers to reach a normal range of 7.1 to 7.2. H_2S decreases the intracellular pH and activates K_{ATP} channels through activating chloride-bicarbonate exchanger (CBE)[8].

Metabolic changes is another way for H_2S to cause a vasorelaxant effect. *In vivo* and *in vitro* studies showed that H_2S and NO inhibit cytochrome c oxidase, the terminal enzyme in the mitochondrial respiratory chain [16].

Also, H_2S works through endothelium-dependent mechanisms, including endothelium-dependent activation of Ca^{2+} sparks and H_2S as an endothelium derived hyperpolarising factor (EDHF) candidate. Following endothelium removal with saponin, it has been reported that the half maximal inhibitory concentration (IC_{50}) of H_2S-induced relaxation of phenylephrine precontracted aorta was increased, indicating that H_2S-induced vasorelaxation is facilitated by the endothelium[17].

The first endothelium-dependent mechanism of H_2S is the activation of Ca^{2+} spark. There are three Ca^{2+} activated K+ channels present in the vascular endothelium, including BK_{Ca}, $K_{Ca}2.3$ (also named SK3) and $K_{Ca}3.1$ (also named IK) channels [18]. In the endothelium of rat mesenteric arteries, H_2S activates BK_{Ca} and IK_{Ca}/SK_{Ca} channels, leading to hyperpolarisation of the endothelial cell membranes, in which calcium influx is enhanced through non-voltage-gated calcium channels, leading to increase in endothelial cell calcium and activation of cytochrome P450 epoxygenase and transient receptor potential (TRP) channels to increase Ca^{2+} sparks in vascular smooth muscle cells causing vasorelaxation[19].

H_2S effect on vascular smooth muscle cell proliferation

H_2S plays an important role in modulating vascular smooth muscle cell proliferation and apoptosis that is important to maintain vascular structure and function. In CSE gene deficient knock out mice, the absence of endogenous H_2S in vascular smooth muscle cells (VSMC) showed a significant surge in growth rate. In cultured smooth muscle cells and in the me-

dia of the aorta, the percentage of BrdU-positive cells was higher with CSE knock out (KO) mice than age-matched CSE wide type (WT) mice[1]. So, the endogenous CSE/H_2S limits the smooth muscle cell proliferation and growth. Moreover, the blood pressure of CSE KO mice was normalised by captopril showing that the proliferation is not secondary to hypertension in these mice when compared to untreated CSE KO mice[20]. Another study found that in human aortic smooth muscle cells, NaHS at a concentration of 200µM induced apoptosis[21]. After PPG pre-treatment or knocking down endogenous CSE gene, which inhibits H_2S, NaHS pro-apoptotic effect became significant at 50-100µM. Another study showed that NaHS at a concentration of 100µM induced apoptosis and inhibited proliferation of VSMC of KO, but not WT mice[20].

The anti-proliferative and pro-apoptotic effect of H_2S is multifaceted. It involves the mitogen activated protein kinase (MAPK) superfamily, including three parallel cascades: stress activated protein kinase/c-Jun NH_2 terminal kinase (SAPK/JNK) cascade, the p38-MAPK cascade and the classical extracellular signaling regulated kinase (ERK)/MAPK cascade. H_2S induced apoptosis in human aortic smooth muscle cell, for example, via activation of MAPK pathway. The apoptotic signal is converted to its downstream enzyme cascades by the phosphorylation of ERK which then activates caspase-3. After the inhibition of ERK and caspase-3 activities, the H_2S induced apoptosis of human aortic smooth muscle cell was attenuated[22].

H_2S effect on vascular endothelial cell proliferation

In cultured human umbilical vein endothelial cells (HUVECs) and bEnd3 microvascular endothelial cells, it has been reported that H_2S has a stimulatory effect. possibly through stimulation of phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway, K_{ATP} channels, MAPK and the inhibition of guanylate cyclase-c/cyclic guanosine monophosphate (sGC/cGMP) pathway[23]. It has also been reported that in cultured human saphenous vein endothelial cells, intracellular calcium concentration was increased by NaHS administration[24]. The release of calcium from ryanodine receptor coupled endoplasmic reticulum leads to this increase in intracellular Ca^{2+}. To a smaller extent, this increase is also due to capacitative calcium entry. Additionally, endothelial cells are protected from different stress damage by H_2S. Endothelial cell viability is decreased by hyperglycemia that increases the oxidative stress and nuclear DNA injury[1]. This hyperglycemia stress leads to impaired endothelium dependent vasorelaxation. Exogenous H_2S suppresses the hyperglycemia-induced endothelial cell damage in cultures of microvascular endothelial cells. In the same hyperglycemic culture condition, the viability of endothelial cells is increased by the over-expression of CSE, compared to native endothelial cells. On the other hand, the hyperglycemia-enhanced oxidative stress of endothelial cells was inhibited by siRNA which knocked down the expression of endogenous CSE[25].

Pathophysiological role of H_2S in cardiovascular disorders

H_2S in hypertension

H_2S deficiency may contribute to hypertension pathogenesis. A considerable body of evidence demonstrates involvement of H_2S in blood pressure regulation. The development of hypertension could be linked to a decrease in CSE activity, a reduction of H_2S production or a deficiency in circulating H_2S levels in plasma[26]. Zhao and colleagues (2001) demonstrated that high concentrations of H_2S donors, (> 10 µmol/kg), significantly reduced blood pressure. On the other hand, another study showed that low concentration of H_2S donors (< 10 mmol/kg) increased blood pressure[27]. An *in vivo* experiment showed a vasopressor effect only after the injection of 3 µmol/kg sodium sulfide (Na_2S) intravenously[5], while at higher concentrations of 8-30 mmol/kg, a transient biphasic effect on blood pressure was observed[28].

The main mechanism of the beneficial action of H_2S in hypertension is via induction of vasorelaxation.

In two-kidney-one-clip (2K1C) rat, representing a model of renovascular hypertension that is characterised by an increase in renin production and plasma levels, intra-peritoneal administration of NaHS reduced the development of hypertension. In these animals, plasma renin activity and release were reduced by NaHS administration. This reduction was mediated by the inhibition of both adenylate cyclase activity and cAMP synthesis. On the other hand, in normal one-kidney-one-clip (1K1C) rat, NaHS affected neither blood pressure nor plasma renin activity[29].

Moreover, H_2S reacts with ions in metalloproteins. A study showed that H_2S directly inhibits the activity of angiotensin converting enzyme (ACE) by interfering with the zinc atom in the active center of ACE in cultured human umbilical vein endothelial cells. Subsequently, H_2S reduced angiotensin II production and inhibited bradykinin release[30]. Additionally, NaHS reduced blood pressure by reducing the

affinity of angiotensin II to angiotensin I receptors.

These studies suggest that the inhibition of different components of the renin angiotensin system (RAS) could have an important role in mediating the anti-hypertensive effect of H_2S. In support of this notion, an *in vivo* study showed that H_2S donor induced a decrease in blood pressure that was reduced by the administration of bolus captopril, an ACE inhibitor, suggesting that it may inhibit the mechanism responsible for the depressor effect of H_2S[28].

H_2S in atherosclerosis

Studies have shown that H_2S is decreased in atherosclerosis models[31,32]. In sclerotic aortic tissues, the endogenous H_2S production was impaired due to the decrease in CGL expression in VSMCs[33]. However, the progression of atherosclerosis was slower in the case of H_2S over-production, e.g.: Triasomy 21[34]. Vascular endothelial cell proliferation and migration, microvessel formation, and the healing of wound and ulcers were increased by H_2S *in vivo* and *in vitro*. The proliferation of PKB/AKT, ERK, p38, and the activation of K_{ATP} channels could mediate the pro-angiogenic effect of H_2S[3].

Recent studies showed that the alteration in H_2S metabolism is involved in the initiation and progression of atherosclerosis. In apolipoprotein E KO mice, atherosclerosis occurred with decreased H_2S levels in the blood. The treatment of these mice with NaHS attenuated the thickening and stiffness of the vessels[35]. CSE KO mice were fed on an atherogenic paigen type diet for 12 weeks developed early fatty streak lesions in the aortic root, increased oxidative stress and expression of adhesion molecules, and enhanced aortic intimal proliferation. On the other hand, both WT mice who fed on the same atherogenic diet and CSE KO mice fed a normal diet did not develop any atherosclerotic damage [36].

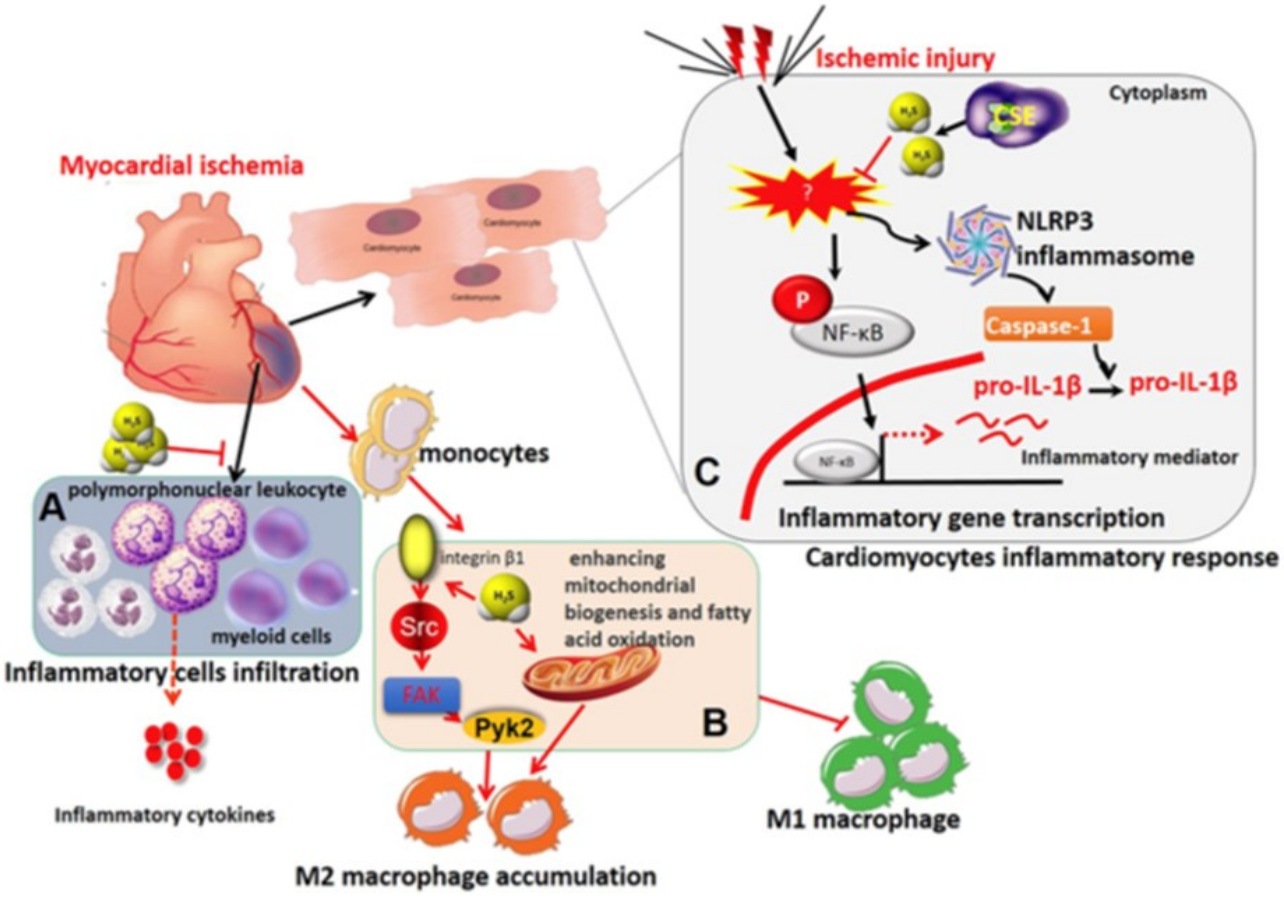

Figure 2. The immunomodulatory role of H_2S in myocardial ischemia. (A) H_2S suppresses $CD11b^+Gr\text{-}1^+$ myeloid cells and polymorphonuclear leukocytes recruitment to the ischemic site, leading to the release of cytokines. (B) Mitochondrial biogenesis and fatty acid oxidation are induced by recruiting macrophages and inducing M2 macrophages. (C) H_2S inhibit the inflammatory response in the ischemic site by inhibiting NF-kB and NLRP3 inflammasome. – IL-1b: interleukin-1b; NLRP3: nucleotide-binding domain, leucine rich-containing family, pyrin domain-containing-3; TNFA: tumor necrosis factor-a. Taken from ref 40.

LDL, vascular calcification, and vascular inflammation; and the suppression of the adhesion of monocytes to endothelial cells [36,37].

H_2S in myocardial ischemia and infarction

It has been found that decreased plasma levels of H_2S were associated with an increased infarct size and mortality[38]. In rats, the infarct size of the left ventricle and the mortality after myocardial infarction (MI) were significantly decreased by NaHS administration. It has also been found that S-propargyl-cysteine, a novel modulator of H_2S endogenously, protects against MI by reducing the deleterious effect of oxidative stress through increased CSE activity and plasma H_2S levels[38]. Moreover, it has been observed that H_2S levels were elevated in ST-elevation acute MI patients[39]. The mechanism of H_2S in cardioprotection has yet to be clarified, but may be attributed to a number of mechanisms, including vasodilation, anti-inflammatory, anti-apoptosis, antioxidant and modulation of cellular metabolism[40].

H_2S plays an important role in the immune-inflammatory process, since MI and reperfusion injury trigger inflammatory leukocyte infiltration and release of cytokines, including interleukin (IL)-6, IL-8, and TNF-a[40]. H_2S treatment suppresses the recruitment of $CD11b^+$ $Gr\text{-}1^+$ myeloid cells and polymorphonuclear leukocytes to ischemic myocardium and releases cytokines such as TNF-A and IL-1b, leading to protection against ischemia injury[40]. In ischemia stimulated cardiomyocytes, the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and nucleotide-binding domain, leucine rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome, inflammatory mediators, and inflammatory response were all inhibited by H_2S[40] (Fig 2).

H_2S in heart failure

H_2S slowed the progression to adverse remodeling of the left ventricle and induced angiogenesis in the myocardium, in a hypertension-induced heart failure model[41]. H_2S attenuated the left ventricular remodeling and dysfunction by creating a pro-angiogenesis environment for the new vessels to grow[42]. In another model of heart failure that is induced by pressure overload, Na_2S administered to mice enhanced pro-angiogenesis factors including matrix metalloproteinase (MMP)-2. Na_2S also suppressed anti-angiogenesis factors such as MMP-9[38].

Moreover, H_2S improved cardiac function,

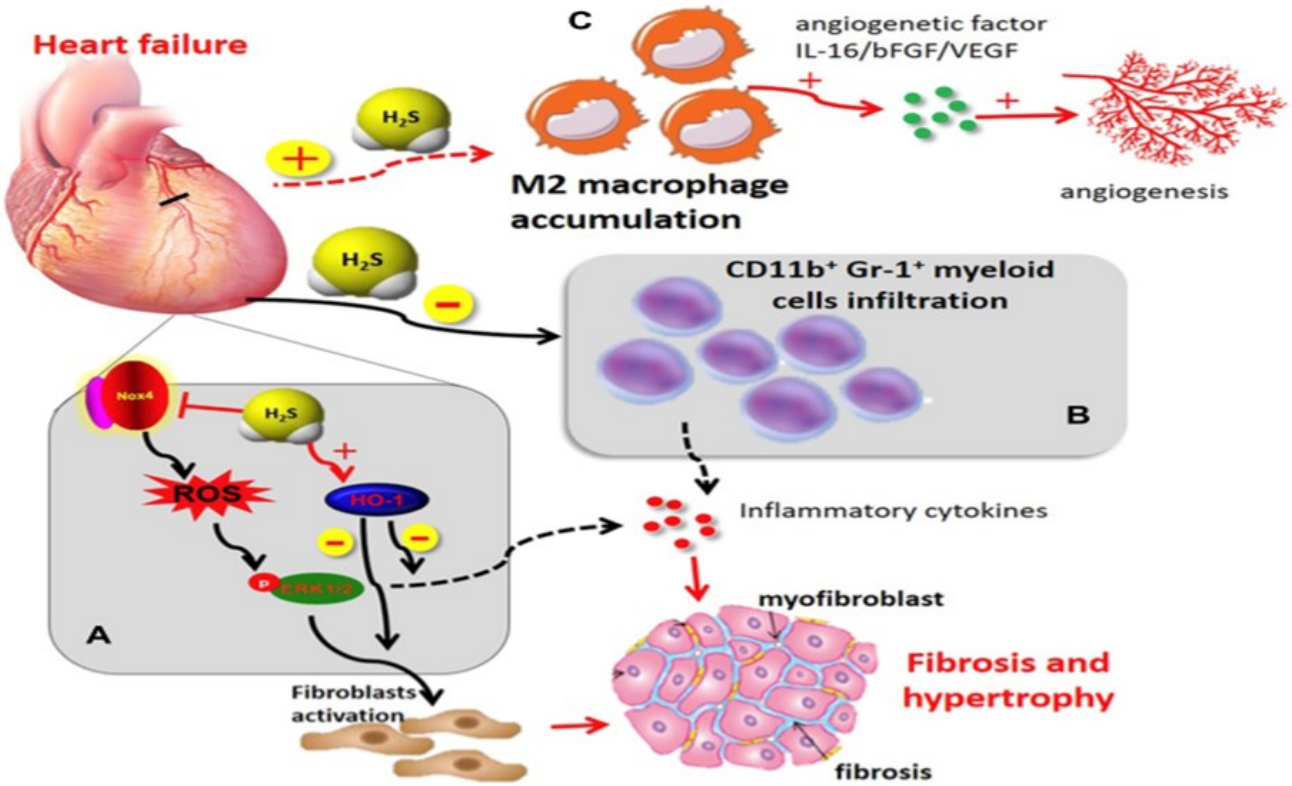

Figure 3: The immunomodulatory role of H_2S in heart failure. (A) H_2S decreases Nox4/ROS/ERK1/2 signaling axis and increases HO-1 expression. (B) H_2S reduces the inflammatory cytokine release by inhibiting the recruitment of $CD11b^+Gr\text{-}1^+$ cells. (C) H_2S releases angiogenesis factor by inducing M2 macrophages polarization. ERK1/2: extracellular signal-regulated kinase 1/2; HO-1: hemeoxygenase-1; Nox-4: NADPH oxidase 4; ROS: reactive oxygen species. Taken from Ref 40.

attenuated myocardial fibrosis and inhibited chronic inflammatory mediators, leading to cardio -protection in heart failure patients[40]. Furthermore, H_2S decreases nicotinamide adenine dinucleotide phosphate hydrogenase oxidase 4 (Nox4)/ROS/ ERK1/2 signaling axis and increases HO-1 expression[40]. A description of H_2S role in heart failure is illustrated in Fig 3.

Novel H_2S based therapeutics

Target therapeutics

Na_2S and NaHS were the first donors to be studied in the cardiac system and reported to have a potential therapeutic effect. They rapidly increase the concentration of H_2S within seconds, but they also rapidly decline in the tissue. Synthetic H_2S-releasing compounds have been developed. GYY4137, a slow-releasing H_2S donor, has been reported to protect against cytotoxicity, which is induced by high glucose levels, by the activation of the AMP-activated protein kinase/mammalian target of rapamycin (AMPK/mTOR) signal pathway in H_9C_2 cells[38]. Moreover, in spontaneously hypertensive rats, GYY4137 was shown to have an anti-hypertensive effect[3]. It also attenuated the inflammation through reducing the circulating pro -inflammatory cytokines and mediators.

Another example of synthetic H_2S donors is SG-1002, a polyvalent sulfur, which is released in a more precisely controlled manner[38]. Pre-clinical studies confirmed that SG-1002 decreased infarct size, improved cardiac function, increased angiogenesis, decreased inflammation, and down-regulated oxidative stress after infarction[3]. In phase one clinical trials of SG-1002, doses of 200, 400 and 800mg in healthy volunteers with increasing levels of H_2S showed minor adverse events[3]. Furthermore, SG-1002 therapy resulted in cardio-protection in heart failure, which is induced by pressure overload, through the up-regulation of the VEGF-Akt-rNOS-NO-cyclic guanosine monophosphate pathway with preserved mitochondrial function, attenuated oxidative stress,- and increased myocardial vascular density[38].

Future directions

Many experimental studies are being conducted on the role of H_2S modulation in the cardiovascular system. The precise molecular targets remain to be fully identified. In near future. One aim is organ-specific delivery of H_2S, but there are organ specific issues that need to be considered[3]. Since H_2S has a wide range of physiological and pathophysiological effects, its delivery will produce a wide range of biological activities. Therefore, the amount and the speed of H_2S release from its donors should be controlled[40]. The development of pH-, oxygen-, and free radical-sensitive donors will help in the targeted delivery of H_2S[3].

Summary

In summary, H_2S affects the cardiovascular system, leading to a negative chronotropic and inotropic effect on the heart. It also induces vasorelaxation through its action on K_{ca} channel, K_{ATP} channel, K_v channel, and ER/SR calcium release channel. H_2S also affects the proliferation of vascular smooth muscle cells and vascular endothelial cells. Due to these effects, H_2S has been shown to be beneficial in the treatment of hypertension, atherosclerosis, ischemia and heart failure. With more understanding of the physiological benefits of H_2S, its cardioprotective properties can be utilised as a potential target at the clinical level.

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TEST YOUR KNOWLEDGE

Answers on back page

1. The amino acid source of H_2S in the human body is:

a) Methionine
b) Alanine
c) Serine
d) Tryptophan

2. The mechanism by which H_2S anti-atherosclerotic effect is manifested is:

a) Inhibition of neointemal hyperplasia
b) Smooth muscle proliferation
c) Decreased level of oxidized LDL
d) All of the above

3. The main mechanism of the beneficial action of H_2S in hypertension is via:

a) Vascular calcification
b) Vasorelaxation
c) Vascular inflammation
d) All of the above

Is there a problem?

A child was given the following drug for pain and fever. Is there any major error with the prescription?

RMX HOSPITAL

Patient Name: Faizal Age: 3 years
Address: Street No: 438

Rx

Paracetamol suspension 250mg/5ml
5ml every 6 hours x 4 days
Send one bottle

Dr. Robert
Signature Date: 1/9/18

Answer (Prescription Exercise)

The prescribed dose of 250mg in 5ml is overdose. For a 3-year-old child with pain and fever, the recommended dose is 180mg every 4-6 h; maximum 4 doses per day.

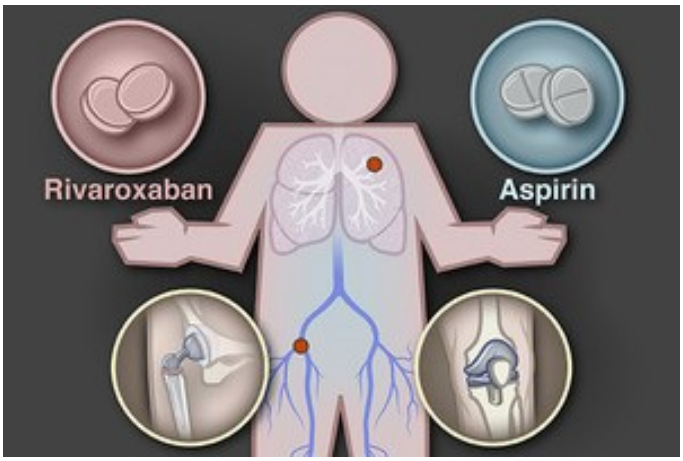
Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Venous thromboembolism prophylaxis after hip or knee arthroplasty: aspirin or rivaroxaban?

It has been suggested by clinical trials and meta-analyses that aspirin may be effective for the prevention of venous thromboembolism, which includes proximal deep-vein thrombosis or pulmonary embolism, after total hip or total knee arthroplasty. However, the literature lacks comparisons with direct oral anticoagulants are for prophylaxis beyond hospital discharge. There's a risk of blood clots in the legs or lungs after knee or hip replacement surgery. So it's routine for patients to take clot-preventing drugs for some time afterwards.

According to a new clinical trial, good old aspirin is just as effective as newer, expensive drugs at preventing blood clots after hip or knee replacement. Researchers claim that the findings could change some doctors' prescribing habits. The trial was funded by the Canadian government. The results were published in the *New England Journal of Medicine*.



https://www.nejm.org/doi/full/10.1056/NEJMoa1712746

Currently, some physicians choose powerful anti-clotting drugs like dabigatran (Pradaxa) and rivaroxaban (Xarelto), according to the trial researchers. But it isn't clear whether those expensive prescription drugs are any better than cheaper readily available aspirin. The recent findings claim they may not be.

Few patients in the study developed a blood clot after surgery, and those on aspirin fared just as well as those on rivaroxaban. The caveat was that all study patients received rivaroxaban for the first five days after surgery. After that, they either continued on rivaroxaban or switched to aspirin for another 9-30 days. From this study there is no evidence to support starting aspirin on day one. But after day five, it's very reasonable to consider switching to aspirin.

Over the past 10 years, surgeons have already been turning away from powerful anticoagulants toward aspirin and non-drug options for stopping clots. These days, patients have a generally low risk of blood clots after hip or knee replacement for a number of reasons, such as shorter surgical times, and the use of regional anesthesia instead of general. Clots can also be prevented by improving blood flow in patients' legs right after surgery. So getting patients on their feet and moving early on is the key. Similarly, pneumatic compression devices can be used to encourage blood flow in the lower limbs while patients are in their hospital beds.

The American Academy of Orthopaedic Surgeons (AAOS) guidelines already state that no one drug is better than another for preventing clots. This study reinforces that. Most people can have just aspirin, but some at high risk of blood clots - those with a history of clots, people who are very obese - might need an anticoagulant. The strategy for preventing clots should include medication and early mobilisation.

The new study involved more than 3,400 patients undergoing hip or knee replacement at any of 15 Canadian hospitals. All took rivaroxaban, a once-daily pill, for 5 days. After that, they were randomly assigned to remain with the drug or switch to low-dose aspirin (81mg/day). Knee replacement patients took their medication for 9 days. Hip replacement patients took it for 30 days. Over 3 months, just over 0.6% of aspirin patients developed a blood clot serious enough to cause symptoms. That was true for 0.7% of rivaroxaban patients.

One risk with any clot-preventing drug is that it can cause bleeding - in the stomach, for instance, or in the brain. In this trial, about 1% of patients in both groups had a bleeding complication. In all cases, it was bleeding at the surgical site. So neither drug appeared better than the other - but aspirin has some obvious advantages as it doesn't require a prescription, and it's inexpensive.

In the study, patients who were already taking low-dose aspirin before they had a hip or knee replacement had their usual aspirin dose temporarily

doubled after surgery. But, there was no evidence that this was more effective at preventing clots. So the researchers' recommendation would be for those patients to return to their usual aspirin regimen, rather than doubling the dose.

In general, patients facing a hip or knee replacement should talk to their surgeon about their personal risk of blood clots, and what measures will be taken to lower it.

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Antidepressants do work, but some are better than others

A large research review has found that antidepressant drugs actually do help ease depression, countering debate over whether the medications do what they're supposed to. However, some antidepressants are more effective and better tolerated than others.

Prescription of these agents should be informed by the best available evidence. Therefore, the authors of the study aimed to update and expand their previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder. They did a systematic review and network meta-analysis, analysing data from 522 trials, published and unpublished, that included more than 116,000 participants. Of the 21 antidepressants studied, all of them worked better than a placebo.

In the short-term, antidepressants seem to work modestly for acute depression. They do have some benefit, on average, but they are not a panacea and need more effective interventions.

Of the many antidepressants, which are sold in the United States, the study found to be most effective included, Amitriptyline, Effexor (venlafaxine), Lexapro (escitalopram), Paxil (paroxetine), Remeron (mirtazapine), Trintellix (vortioxetine). Those that made the least effective list of antidepressant drugs sold in the United States included Luvox (fluvoxamine), Oleptro (trazodone), Prozac (fluoxetine). When the researchers checked which depression drugs were tolerated the best, these topped the list; Celexa (citalopram), Lexapro (escitalopram), Prozac (fluoxetine), Trintellix (vortioxetine), Zoloft (sertraline). The drugs that were found to be less well-tolerated included Amitriptyline, Anafranil (clomipramine), Cymbal-

https://medicine.wustl.edu/news/hard-treat-depression-seniors-focus-13-5-million-study/

ta (duloxetine), Effexor (venlafaxine), Luvox (fluvoxamine), Oleptro (trazadone).

The study authors wrote that there's been "a long-lasting debate and concern about antidepressants' efficacy and effectiveness, because short-term benefits are, on average, modest and because long-term balance of benefits and harms is often under-studied." However, this review shows that "all of these medications can be effective in treating depression, but there's no hands-down winner." If one is looking for the most tolerable and the most effective, Lexapro and Trintellix are the ones listed. While amitriptyline was on the most-effective list, it was also on the least-tolerated list, and he said it's generally not considered a first-line drug for depression treatment.

The differences between the medications were small, and so even medications on the less-effective list might work very well for some people. That's another issue with antidepressant medications. What works well for one person doesn't always work well for another, so there may be some trial and error involved in finding the right medication. It's also important to be sure that one is getting the right dose of medicine and that the drug is taken for long enough to give it time to work well, which can be as long as four to six weeks. However, whenever possible, people with depression shouldn't rely on medications alone but should take psychotherapy with medications.

The authors concluded that antidepressants were more efficacious than placebo in adults with major depressive disorder. Smaller differences between active drugs were observed when placebo-controlled trials were included in the analysis, whereas there was more variability in efficacy and acceptability in head-to-head trials. They recommend that these results should serve evidence-based practice and inform patients, physicians, guideline developers, and policy makers on the “relative merits of the different antidepressants”. It has to be noted that this study looked only at responses after eight weeks of treatment. It was not assessed as to how these medications might work for people taking them for years.

The study was published online February 21 in *The Lancet*.

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NEWS from the FDA

FDA authority over cosmetics

The US law does not require cosmetic products and ingredients, other than colour additives, to have FDA approval before they go on the market, but there are laws and regulations that apply to cosmetics on the market in interstate commerce.

The two most important laws pertaining to cosmetics marketed in the US are the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Fair Packaging and Labeling Act (FPLA). FDA regulates cosmetics under the authority of these laws.

1. What kinds of products are “cosmetics” under the law?

The FD&C Act defines cosmetics by their intended use, as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance" (FD&C Act, sec. 201(i)). Among the products included in this definition are skin moisturisers, perfumes, lipsticks, fingernail polishes, eye and facial makeup, cleansing shampoos, permanent waves, hair colors, and deodorants, as well as any substance intended for use as a component of a cosmetic product. It does not include soap.

2. What does the law say about the safety of cosmetics?

The FD&C Act prohibits the marketing of adulterated or mis-branded cosmetics in interstate commerce. “Adulteration” refers to violations involving product composition--whether they result from ingredients, contaminants, processing, packaging, or shipping and handling. Under the FD&C Act, a cosmetic is adulterated if

"it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under conditions of use as are customary and usual" (with an exception made for

coal-tar hair dyes);
"it consists in whole or in part of any filthy, putrid, or decomposed substance";
"it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health";
"its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health"; or
except for coal-tar hair dyes, "it is, or it bears or contains, a color additive which is unsafe within the meaning of section 721(a)" of the FD&C Act. (FD&C Act, sec. 601)

3. Does FDA approve cosmetics before they go on the market?

FDA's legal authority over cosmetics is different from our authority over other products FDA regulates, such as drugs, biologics, and medical devices. Under the law, cosmetic products and ingredients do not need FDA premarket approval, with the exception of color additives. However, FDA can pursue enforcement action against products on the market that are not in compliance with the law, or against firms or individuals who violate the law.

4. Who is responsible for substantiating the safety of cosmetics?

Companies and individuals who manufacture or market cosmetics have a legal responsibility to ensure the safety of their products. Neither the law nor FDA regulations require specific tests to demonstrate the safety of individual products or ingredients. The law also does not require cosmetic companies to share their safety information with FDA. FDA has consistently advised manufacturers to use whatever testing is necessary to ensure the safety of their products and ingredients.

5. Can FDA order the recall of a hazardous cosmetic from the market?

Recalls of cosmetics are voluntary actions taken by manufacturers or distributors to remove from the marketplace products that represent a hazard or gross deception, or that are somehow defective (21 CFR 7.40(a). FDA is not authorized to order recalls of cosmetics, but they do monitor companies that conduct a product recall and may request a product recall if the firm is not willing to remove dangerous products from the market without FDA's written request.

6. What actions can FDA take against companies or individuals who market adulterated or mis-branded cosmetics?

FDA may take regulatory action if they have reliable information indicating that a cosmetic is adulterated or misbranded. For example, FDA can pursue action through the Department of Justice in the federal court system to remove adulterated and misbranded cosmetics from the market. In addition, FDA works closely with U.S. Customs and Border Protection to monitor imports.

7. Can FDA inspect cosmetics manufacturers?

FDA can and does inspect cosmetic manufacturing facilities to assure cosmetic product safety and determine whether cosmetics are adulterated or mis-branded under the FD&C Act or FPLA.

8. Does FDA test cosmetics or recommend testing labs?

Although FD&C Act does not subject cosmetics to premarket approval by FDA, they do collect samples for examination and analysis as part of cosmetic facility inspections, import inspections, and follow-up to complaints of adverse events associated with their use. FDA may also conduct research on cosmetic products and ingredients to address safety concerns.

9. Do cosmetics firms need to register with FDA or get an FDA license to operate?

Under the law, manufacturers are not required to register their cosmetic establishments or file their product formulations with FDA, and no registration number is required to import cosmetics into the United States.

Reference

https://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074162.htm

Cosmetics– FDA authority

* **Cosmetics must not be adulterated or mis-branded**
* **US law does not provide for FDA pre-market approval**
* **FDA's authority is post-market only**

IN THE NEWS

European panel (CHMP) endorses three cancer drugs

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has newly endorsed two haematologic cancer drugs and one drug for neuroendocrine tumours (NETs). All three drugs now move onto review and possible approval from the European Commission.

CHMP adopted a positive opinion for everolimus (*Afinitor*,Novartis) for the treatment of unresectable or metastatic, well-differentiated (grade 1 or 2), non-functional NETs of gastrointestinal (GI) or lung origin in adults with progressive disease.

There is an unmet need in this setting because there are currently few or no treatment options in Europe for these patients. Everolimus was approved earlier in 2016 by the US FDA for the same use. The recommendation of everolimus in Europe is based on efficacy and safety data from the pivotal phase 3 RADIANT-4 study, in which everolimus reduced the risk for progression in patients with progressive, well-differentiated, non-functional, locally advanced or metastatic NETs of GI or lung origin by 52%, compared with placebo. Median progression-free survival was 7.1 months longer with everolimus than with placebo (11 *vs* 3.9 months). The most common treatment-related grade 3/4 adverse events (≥5%) for everolimus and placebo, respectively, were stomatitis (9% vs 0%), diarrhea (7% vs 2%), and infections (7.0% vs 0.0%). The most common treatment-related adverse events of any grade (incidence ≥10%) were stomatitis (63%), diarrhea (31%), fatigue (31%), infections (29%), rash (27%) and peripheral edema (26%).

Recommendations in hematologic cancers

CHMP also recommended broadening the existing marketing authorisation for ibrutinib (*Imbruvica*, Janssen/Pharmacyclics) for the first-line treatment of adults with chronic lymphocytic leukemia (CLL).

Ibrutinib is already approved for the treatment of adults with relapsed or refractory mantle cell lymphoma, for the treatment of adults with CLL who have received at least one previous therapy, or for first-line treatment of patients with a 17p deletion or *TP53* mutation who are unsuitable for chemo-immunotherapy. It is also indicated for use in patients with Waldenström's macroglobulinemia.

The new recommendation is based on data from the phase 3 randomized open-label RESONATE-2 trial, which compared ibrutinib with chlorambucil in treatment-naïve patients. The rate of progression-free survival at 18 months was better with ibrutinib than with chlo rambucil (90% *vs* 52%). Overall survival was significantly prolonged with ibrutinib. In fact, at 24 months, overall survival was 98% with ibrutinib and 85% with chlorambucil.

Google image

The safety of ibrutinib was consistent with previously reported studies. The most common adverse events (≥20%) of any grade in the RESONATE-2 trial for ibrutinib were diarrhea (42%), fatigue (30%), cough (22%), and nausea (22%). Ibrutinib was approved by the FDA in March 2016 for the first-line treatment of CLL.

Finally, CHMP recommended extending the authorised indication of obinutuzumab (*Gazyvaro*, Roche) to patients with follicular lymphoma who were previously treated with chemotherapy. Obinutuzumab is to be used in combination with bendamustine. Obinutuzumab was first approved in Europe in 2014 for use in combination with chlorambucil in patients with previously untreated

CLL. Both follicular lymphoma and CLL affect B -lymphocytes. The new recommendation is based on the results from a phase 3 trial that compared obinutuzumab in combination with bendamustine (and followed by obinutuzumab as a maintenance treatment) with bendamustine alone in 321 patients with follicular lymphoma who did not respond to or whose disease progressed with chemotherapy. Median progression-free survival was longer in patients treated with obinutuzumab plus bendamustine than in those treated with bendamustine alone (29 *vs* 14 months). The most common adverse effects reported with the combination of obinutuzumab plus bendamustine were consistent with the known safety profiles of the individual medicines.

Obinutuzumab was approved by the FDA for follicular lymphoma.

Source

http://www.medscape.com/viewarticle/862661?nlid=104473_1842&src=WNL_mdplsfeat_160503_mscpedit_wir&uac=118197BN&spon=17&impID=1083608&faf=1

Clot-buster for stroke- Tenecteplase vs Alteplase

After a stroke, many patients are given the thrombolytic, drug alteplase, but another drug may be more effective, according to a group of Australian researchers. Their study showed that tenecteplase was about twice as effective as alteplase, and had less disability. Tenecteplase is likely to become the preferred medication for dissolving clots in stroke. It is also likely to change stroke treatment guidelines and clinical practice. Both drugs work in the same way, but tenecteplase is better at attacking and dissolving clots, and more resistant to factors that inhibit the breakdown of clots.

For either drug to be most effective, it needs to be given as soon as possible after a stroke occurs. In 2000, the U.S. FDA approved tenecteplase for use after a heart attack.

It is being widely used in developing countries such as India, also due to its lesser cost. Additionally, tenecteplase can be given as a single injection, while alteplase requires an injection and an IV drip.

The researchers in this study conducted an investigator-initiated, multicenter, prospective, randomised, open-label, blinded-outcome trial with patients who had ischemic stroke within 4.5 h after onset. They also had large-vessel occlusion of the internal carotid, middle cerebral, or basilar artery and who were eligible to undergo intravenous thrombolysis and endovascular thrombectomy. They enrolled patients at 13 centers in Australia and New Zealand.

More than 200 patients were randomly allocated, in a 1:1 ratio, to receive intravenous tenecteplase (at a dose of 0.25 mg/kg body weight; maximum dose, 25 mg) or alteplase (at a dose of 0.9 mg/ kg; maximum dose, 90 mg).

The primary outcome was substantial reperfusion which was defined as the restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial assessment. If intracranial angiography could not be performed, the primary outcome was assessed as reperfusion of at least 50% of the involved territory 1 to 2 h after thrombolysis.

They also determined which drug was better at restoring blood flow to clot-blocked blood vessels in the brain, and which drug resulted in patients having better outcomes. They found that 22% of the patients treated with tenecteplase had more than 50% of blood flow return to the brain, compared with 10% of those treated with alteplase. The tenecteplase group also had better functional outcomes after 90 days than those given alteplase.

With regard to adverse effects, intracerebral hemorrhage or bleeding into the brain, the most serious side effect of either drug, occurred in 1% of patients, regardless of which drug they received. There were 10 deaths in the tenecteplase group and 18 in the alteplase group but this difference was statistically not significant.

A limitation of the trial is that the findings are applicable to patients with ischemic stroke and large-vessel occlusion, who are eligible for thrombolysis-representing only about 13% of all patients with ischemic stroke.

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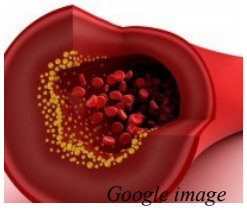

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STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from June to August 2018

Amorosinal Nail Lacquer 5%; Amorolfine (as HCl) 5%; Al Mufid; Chanelle Medical Ireland

Bendamustine Hydrochloride Accord Powder for Concentrate for Soln.for Infn. 25 and 100mg; Bendamustine Hydrochloride 25 and 100mg/Vial; Al Hajery; Accord Healthcare Limited/UK

Besponsa Powder for soln. for Infn. 0.9mg/Vial; Inotuzumab Ozogamicin (r DNA); Safwan; Wyeth Pharma/Sub. of Pfizer Inc./USA

Evoxil Solution for Infusion 5mg/ml; Levofloxacin (as hemihydrate) 5mg; Al-Hajery; Pharmathen Hellas S.A./Greece

Gemcitabine 0.2, 1 and 2g Powder for Solution for Infusion; Gemicitabine HCl 0.2, 1 and 2g; Al Hajery; Accord Healthcare Limited/UK

Gestophil Vaginal Suppositories 400mg; Progesterone 400mg; Synergy Health; Philadelphia Pharmaceuticals/Jordan

Hemlibra Solution for Injection 30, 60 and 150mg/ml and 105mg/0.7ml; Emicizumab; Ali Abdulwahab; F.H. Roche Ltd Switzerland

Lucentis Solution for Injection 10mg/ml PFS; Ranibizumab (rDNA) 10mg/ml; Al-Mojil; Novartis Pharma AG/Switzerland

Monteer Tablets 10/10mg; Atorvastatin (as Calcium) 10mg Amlodipine (as Besylate) 10mg; Al-Hajery; The United Pharm . Man. Co. Ltd./Jordan

Monteer Tablets 5/10mg; Atorvastatin (as Calcium) 10mg Amlodipine (as Besylate) 5mg; Al-Hajery; The United Pharm. Man. Co. Ltd./Jordan

Parsabiv Solution for Injection 2.5, 5 and 10mg; Etelcalcetide (as Hydrochloride) 2.5, 5 and 10mg; Al-Homaizi; Amgen Europe B.V./The Netherlands

Tremfya Sol. for Infn. 100mg/ml; Guselkumab (r DNA); Alghanim Healthcare; Janssen Cilag Int.- Belgium

Verzenio Tablets 50, 100, 150 and 200mg; Abemaciclib 50, 100, 150 and 200mg; Bader Sultan; Eli Lilly USA

Vilasar Tablets 320mg; Valsartan 320mg; Safwan; Dar Al Dawa Dev. & Inv. Co. Ltd./Jordan

Vosevi Tablets; Sofosbuvir 400mg, Velpatasvir 100mg, Voxilaprevir 100mg; Warba; Gilead Sciences International Ltd./UK



Answers to: Test your knowledge

Correct answers:
1-a; 2-d; 3-b

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

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