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Benzyl alcohol and benzoic acid group used as excipients

Report published in support of the 'Questions and answers on benzyl alcohol used as an excipient in medicinal products for human use' (EMA/CHMP/508188/2013) and the 'Questions and answers on benzoic acid and benzoates used as excipients in medicinal products for human use' (EMA/CHMP/508189/2013)



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Executive summary

This document and the related questions and answers documents [23, 24] have been written in the context of the revision of the Annex of the European Commission Guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' [4, 9].

The use of benzoic acid and benzyl alcohol as excipients and mainly employed as solubilising agent and/or preservative in medicinal products. However, in pre-term and full-term neonates, concerns have been raised with the use of benzyl alcohol and benzoic acid. Benzyl alcohol administered intravenously has led to "gasping syndrome" in several pre-term neonates with metabolic acidosis involving deterioration of the neurological state, cardio-vascular failure and haematological anomalies. The majority of poisonings were fatal. This syndrome was associated with the accumulation of benzyl alcohol and its metabolite, benzoic acid. Benzyl alcohol must not be used in pre-term and full-term neonates. It is recommended to revise and implement information on these excipients in the package leaflet of medicinal products.

Introduction

Benzoic acid and benzyl alcohol are aromatic chemical compounds used for the improvement of active substance solubility and added as antibacteriostatic compound. Benzyl alcohol is mainly used in medicinal products wherein the route of administration is parenteral and to a lesser extent topical; whereas the two main routes of administration for benzoic acid are topical and per os.

Scientific discussion

1. Characteristics

1.1. Category (function)

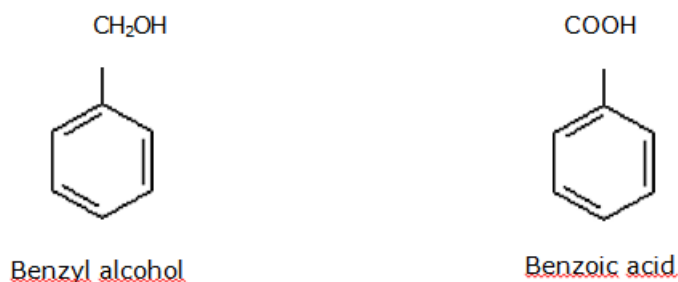
Benzyl alcohol is mainly used as a preservative. The minimal inhibitory concentrations (MIC) are as follows:

Microorganism	MIC* (µg/ml)
Aspergillus niger	5000
Candida albicans	2500
Escherichia coli	2000
Pseudomonas aeruginosa	2000
Staphylococcus aureus	25

* Minimal inhibitory concentration

Benzoic acid is a bacteriostatic antiseptic that is only active in an acidic environment (pH 2.5 to 4.5). It is mainly used as a preservative.

1.2. Physico-chemical Properties



Natural sources of benzyl alcohol are Tolu or Peru Balsam as well as plant extracts such as that of jasmine. Industrial preparation of benzyl alcohol is done by the hydrolysis of benzyl chloride, using the Cannizzaro or the Tischenko reaction starting with benzaldehyde.

It has to be noted that benzyl benzoate, a molecule used as a plasticiser, solubilising agent, solvent or therapeutic agent, generates benzoic acid and benzyl alcohol after hydrolysis.

1.3. Use in medicinal products

Benzyl alcohol is used as both an excipient (preservative, solubilising agent) and as an active principal (antiseptic, local anaesthetic).

Benzyl alcohol is used for different purposes:

- preservative (2% in oral or parenteral pharmaceutical preparations, 3% in cosmetics)
- solubilising agent (concentration greater than or equal to 5%)
- disinfectant (10% solutions)
- local anaesthetic (in certain injections, cough remedies, ophthalmic solutions, ointments, dermatological aerosols)

The most common routes of administration are parenteral and to a lesser extend topical.

Benzyl alcohol is notably used via intramuscular administration in antibiotics, anti-inflammatory products or neuroleptics for its anaesthetic properties, in order to reduce pain at the injection site. The median concentration is 150 mg per injection (30 mg/ml). The range of injected dose varies from 20 to 600 mg/day.

Benzyl alcohol is also used as a preservative and may possibly be substituted by other preservative substances. However, benzyl alcohol also acts as a local anaesthetic, a property that is highly valued for reducing pain associated with intra-muscular injection.

2. Pharmacokinetics

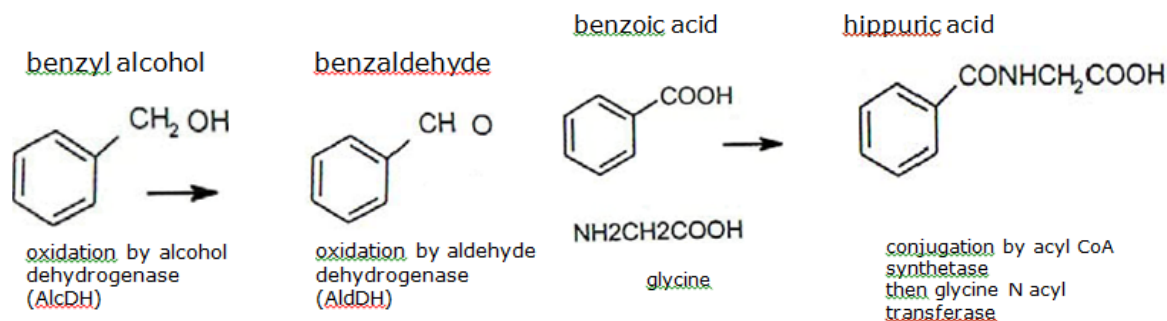
2.1. Absorption

Route of Administration	Absorption	
	Benzyl alcohol	Benzoic acid
cutaneous	Up to 60%	43%

oral	100 %	100%
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The oral absorption is complete. The cutaneous absorption of benzyl alcohol is significant.

2.2. Metabolism



Benzyl alcohol is oxidised by alcohol dehydrogenase (AlcDH), a cytoplasmic enzyme present mainly in the liver, but also in the intestine and kidney. This reaction is saturable. The benzaldehyde formed is oxidised by aldehyde dehydrogenases (AldDH), cytoplasmic and mitochondrial enzymes mainly present in the liver, but also in the intestine and numerous organs.

Secondary metabolism:

Benzaldehyde can react with biogenic amines according to the Pictet and Spengler reaction and lead to the formation of corresponding tetrahydroisoquinolines and beta-carbolines, which are pharmacologically active derivatives.

As benzyl alcohol is quickly metabolized in benzoic acid after administration, it is not present at measurable level in the blood but its oxidation product, benzoic acid, is present and may be used for kinetic.

A perturbation of metabolism (anomaly, $\text{ADH}2^*3$ allelic variant [30] or immaturity) or elimination of benzyl alcohol may lead to toxicity. Indeed, there is a greater accumulation of benzyl alcohol in serum of pre-term neonates expressed in peak level and in area under curve than in full-term neonates [16].

2.3. Elimination

Benzoic acid undergoes conjugation by acyl CoA synthetase then by glycine N acyl transferase to form hippuric acid. The newly synthesised hippuric acid is then eliminated in the urine.

For an adult, after intravenous administration of a dose of 15 mg/kg, the elimination half-life from plasma is 16 minutes for benzoic acid and 31 minutes for hippuric acid. Eighty per cent of the dose is eliminated in the urine in the form of hippuric acid. Clearance is approximately 600 ml/min.

The benzoic acid detoxification process is immature in those pre-term neonates [16] and conjugation of benzoic acid is saturated more quickly. This reaction is furthermore limited by the glycine available. This results in an accumulation of benzoic acid.

3. Toxicology

3.1. Toxicity after single administration of benzyl alcohol

Species (adult animals)	Route	LD50	Observations
rat	orally	1230-3200 mg/kg	
mouse	orally	1580 mg/kg	
rabbit	orally	1040 mg/kg	
rat	IV	50 mg/kg	convulsions, dyspnea, change in behaviour, haemolysis
mouse	IV	324 mg/kg	
rat	SC	1700 mg/kg	
rat	IP	400 mg/kg	
rabbit	Dermal	2000 mg/kg	
Guinea pig	Dermal	<5 mg/kg	
rat	Inhalation	>4.178 mg/l	

3.2. Toxicity after single administration of benzoic acid

Species (adult animals)	Route	LD50*
cat	orally	2 g/kg
dog	orally	2 g/kg
mouse	IP	1.46 g/kg
mouse	orally	1.94 g/kg
rat	orally	1.7 g/kg

* Lethal dose 50%

3.3. Toxicity after repeated administration of benzyl alcohol

Species	Route	Duration	Doses	Observations	NOAEL
Rat adult	orally	16 days	125–2000 mg/kg	Diffuse haemorrhages	M: 250 mg/kg F : 125 mg/kg
Mouse adult	orally	16 days	125–2000 mg/kg	Lethargy, respiratory anomalies	M: 250 mg/kg F: 500 mg/kg

Rat adult	orally	13 weeks	50–800 mg/kg	Neurotoxicity, respiratory difficulties, diffuse bleeding, necrosis of the brain, muscles, thymus congestion, renal haemorrhages and damage	100 mg/kg
Rat adult	orally	103 weeks	200–400 mg/kg	Diffuse haemorrhages and neurological lesions	< 200 mg/kg
Rat juvenile (d22)	orally	6 weeks	100–600 mg/kg/d	Gasping syndrome at the higher dose levels	300 mg/kg/d (Foulon, 2005) [7]

No data have been reported for parenteral use, or topical use. Furthermore, there are no chronic studies related to toxicity on newborn or infant animals. There is only one study performed on juvenile rats establishing a NOAEL close to the adult one after oral administration [7].

3.4. Hypersensitivity

Some allergic reactions have been reported in humans. Benzyl alcohol may lead to local reactions (contact dermatitis) and general reactions, probably linked to a direct histamine release [19].

3.5. Local tolerance

Both Benzyl alcohol and Benzoic acid are mucous membrane irritant [28]; it causes serious irritation following application to the skin of mice.

3.6. Genotoxicity

A clastogenic effect has been shown in vitro [20]. However, the results obtained in vivo are negative.

3.7. Carcinogenicity

JECFA (joint FAO/WHO expert committee on food additives) considered that, although long term carcinogenicity and toxicity studies carried out with sodium benzoate in rats and mice were not very good quality, all of the available data, in particular new studies with benzyl acetate, lead to the conclusion that compounds from the benzoic acid family are not carcinogenic [14].

3.8. Reproductive function toxicity

In rats, no action on the growth, fertility, lactation or survival has been observed during a multigeneration reproductive study (because of the consumption of glycine occurring during elimination of benzoic acid and the possibility that glycine is essential for growth, a detrimental effect on growth could be envisaged).

Toxicity on foetal development has only been observed at doses that are toxic to the mother.

Three reproductive studies and 3 developmental toxicity studies exist, which lead to the conclusion that the no observable adverse effect level (NOAEL) after ingestion is in the order of 500 mg/kg/day.

4. Clinical safety data

4.1. Pharmacovigilance

Sixteen neonatal deaths thought to be caused by the benzyl alcohol preservative used in some intravascular solutions have been reported to the Food and Drug Administration (FDA)¹ by 2 medical centres [5, 8]. The deaths occurred in pre-term neonates weighing 2500 g who had central intravascular catheters flushed periodically each day with bacteriostatic normal saline containing 9 mg/ml benzyl alcohol. Ten deaths occurred in 1 institution over a 6-month period and 6 deaths occurred in the other institution over a 16-month period. Investigators in the 2 hospitals have reported that similar deaths have not occurred since flush solutions without preservatives have been substituted for those with the benzyl alcohol.

Onset of toxic illness in the infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial haemorrhage; hypotension leading to cardiovascular collapse was a late finding usually presaging death.

Gas chromatographic analysis demonstrated benzyl alcohol or its metabolites in blood and urine samples from infants in 1 hospital. Retrospective analysis of urine samples from 5 infants in the other hospital for organic acid profile by gas-liquid chromatography showed urine benzoate levels of 4.4–16.1 mg/mg creatinine and hippurate levels of 7.4–33.3 mg/mg creatinine (normal values = 0-trace); serum benzoic acid levels were 8.4–28.7 mEq/L (normal = 0). Review of the medical records of the affected infants resulted in estimates of daily intake of benzyl alcohol ranging from 99 to 405 mg/kg/day.

Data type	Population	Exposure vector	Route	Benzyl alcohol dose	Observations	Reference
Retrospective study	10 premature newborns	catheters* rinsed with heparin and 0.9% benzyl alcohol solutions and Bacteriostatic water used for dilution and reconstitution	IV	99–234 mg/kg/day	gasping syndrome, neurological deterioration, metabolic acidosis, haematological anomalies, hepatocellular insufficiency, renal failure, cardiovascular collapse, 6 out of 10 deaths**	Gershanik, 1981 [8]

¹ FDA WARNING IN 1982: Neonatal Deaths Associated With Use of Benzyl Alcohol - United States

Retrospective study	11 premature newborns	catheters* rinsed with heparin and 0.9% benzyl alcohol solutions and Bacteriostatic water used for dilution and reconstitution	IV	130-405 mg/kg	progressive encephalopathy, convulsions, hypotension, cardiovascular collapse, 10 out of 11 deaths	Brown, 1982 [5]
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* Umbilical catheterisation for monitoring following respiratory distress requiring ventilation

** No new cases have been reported by the authors after having prohibited the procedure of rinsing catheters with benzyl alcohol. The authors conclude that pre-term neonates who receive preparations containing benzyl alcohol intravenously accumulate the alcohol and its metabolites. This accumulation may be explained by the very high doses of benzyl alcohol relative to the size and weight of the neonates, and the reduced metabolic capability in pre-term neonates.

Data type	Population	Exposure vector	Route	Benzyl alcohol dose	Observations	Reference
Retrospective study	Neonates	Amiodarone Atracurium Dexamethasone Glycopyrrolate Phenobarbital Midazolam	continuous or intermittent infusions	0.6–319.5 mg/kg/d	No outcome data described	Shehab, 2009 [29]
Reported case	Pre-term neonate (24w gestation)	Clindamycin	IV	unknown	Desaturation, chest splinting requiring resuscitation	Hall, 2004 [10]
Reported case	Neonate (day 4)	Amiodarone	IV instead of orally	Approximately 20 mg/kg*	Amiodarone contains BA and polysorbate 80, exerting hemodynamic effects. Hypotension requiring cardiopulmonary resuscitation, systemic and peripheral hypoperfusion, lactic acidosis, multiple organ failure (hepatic	Masi, 2008 [18]

					and renal), myocardial ischaemia, encephalopathy.	
Reported case	Girl, 5 year-old	Valium	IV	180 mg/kg/day over 36 hours	Valium contains BA, benzoic acid and propylene glycol, exerting hemodynamic effects, hypotension, metabolic acidosis, death.	Lopez, 1995 [17]
Reported case	Male, 53 years old	Vepesid (etoposide)	IV	90 mg/kg in one perfusion	Haemolysis, metabolic acidosis, death	Smith, 2001 [30]
Reported case	Female, 65 years old	(mupirocin, pimecrolimus cream), prednisone IM and triamcinolone	Cutaneous, IM	Unknown	Chronic conjunctival inflammation and concomitant eyelid dermatitis with ectropion	Jacob, 2008 [11]

* The loading dose (47 mg/kg of amiodarone) was administrated intravenously. Amiodarone (150 mg of amiodarone/ml) contains 20 mg/ml of Benzyl alcohol.

4.2. Conclusion regarding the toxicity of benzyl alcohol

In adults, a single case of toxicity linked to the administration of benzyl alcohol has been reported in the literature even if the role of benzyl alcohol is uncertain. The dose administered was estimated as 90 mg/kg intravenously [30].

The main problem linked to the use of benzyl alcohol concerns neonates (pre-term and full-term) due to the immaturity of the metabolising enzymes and the risk of subsequent accumulation. Benzyl alcohol administered intravenously has led to "gasping syndrome" in several pre-term neonates with metabolic acidosis involving deterioration of the neurological state, cardio-vascular failure and haematological anomalies. The majority of poisonings were fatal. This syndrome is associated with the accumulation of benzyl alcohol. In one case in a five-year-old girl, adverse events occur at 20 mg/kg of benzyl alcohol intravenously although benzyl alcohol was not the only excipient allowing this effect in amiodarone (there was also polysorbate 80).

4.3. Conclusions regarding the toxicity of benzoic acid

All of the data examined have enabled the Acceptable Daily Intake (ADI) to be set at 5 mg/kg orally (in food) for benzoic acid and its salts on the basis of a NOAEL of 500 mg/kg determined during the reprotoxicity studies. The ADI is valid for adults and children over 4 weeks [13].

Benzoic acid may be used for managing hyperammonaemia in urea cycle disorders in the neonates. However, the main problem linked to the use of benzoic acid concerns neonates (pre-term and full-term) who have immature metabolising enzymes leading to accumulation. The risk associated with the

accumulation of benzoic acid is an increase in bilirubinaemia following displacement of bilirubin from albumin and which may cause newborn jaundice to develop into kernicterus [12] (non-conjugated bilirubin deposits in the brain tissue) [2].

5. Updated information for the package leaflet

Benzyl alcohol

Benzyl alcohol is classified in the list of excipients with known effects.

It appears that the table of excipients with known effects is incomplete and erroneous:

- The risk inherent to benzyl alcohol is due to its accumulation in the organism. Elimination of benzyl alcohol is highly variable as both the age (immaturity) and ethnic polymorphism of alcohol dehydrogenase may lead to accumulation of benzyl alcohol and thus toxicity. It is thus difficult to establish an exemption threshold.
- The actual recommendation does not recommend benzyl alcohol for children up to 3 years.

Benzoic acid

Benzoic acid is classified in the list of excipients with known effects.

It appears that the table of excipients with known effects is incomplete and erroneous: there is a risk of jaundice also by oral administration, for which absorption is 100%.

Neither benzyl alcohol nor benzoic acid should be used in neonates (pre-term and full-term).

Benzyl alcohol and benzoic acid should be used with caution for children older than four weeks.

Clinician should be aware of the following:

- Accumulation of benzyl alcohol may lead to toxicity
- Avoid a chronic use
- Use with caution

Therefore the following updated information is proposed:

Benzyl alcohol

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzyl alcohol	All routes of administration	Zero	<p>This medicine contains x mg benzyl alcohol in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.</p> <p>Benzyl alcohol may cause allergic reactions.</p>	
	Oral, parenteral	Zero	<p>Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.</p> <p>Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor.</p>	<p>Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known.</p> <p>Warning in section 4.4 in the SmPC should be given if used in neonates.</p>
			<p>Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.</p>	<p>Increased risk due to accumulation in young children.</p>
			<p>Ask your doctor or pharmacist for advice if you are pregnant or breast feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").</p>	

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
			Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").	High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).
	Topical	Zero	Benzyl alcohol may cause mild local irritation.	

Benzoic acid

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzoic acid (E 210) and benzoates e.g.:	All routes of administration	Zero	This medicine contains x mg <benzoic acid/benzoate salt> in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.	
Sodium benzoate (E 211) Potassium benzoate (E212)	Oral, parenteral	Zero	<Benzoic acid/benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
	Topical	Zero	<Benzoic acid/benzoate salt> may cause local irritation.	May cause non-immunologic immediate contact reactions by a possible cholinergic mechanism.
			<Benzoic acid/benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Absorption through the immature skin of neonates is significant.

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