Ethanol in Herbal Medicinal Products for Children

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Abstract

For some years the safe use of ethanol-containing herbal medicinal products in children has been repeatedly questioned by experts and consumers. On the basis of scientific knowledge the following publication examines the toxicological relevance of ethanol in herbal medicinal products with regard to the ingested amounts, metabolism and elimination in children. The exposition is assessed as compared to food commonly used by children. It is concluded that at recommended doses there is no risk caused by ingestion of ethanol-containing herbal medicinal products. From poison control centres, there are no published reports on intoxications with herbal medicinal products available.

Zusammenfassung

Ethanol in pflanzlichen Arzneimitteln für Kinder

Seit einigen Jahren wird in Fachkreisen und von Verbrauchern immer wieder die Sicherheit der Anwendung pflanzlicher Ethanol-haltiger Arzneimittel bei Kindern in Frage gestellt. Basierend auf wissenschaftlichen Erkenntnissen wird in dem nachfolgenden Beitrag untersucht, welche toxikologische Relevanz dem Ethanol in pflanzlichen Arzneimitteln zukommt. Hierbei werden die eingenommenen Mengen, der Metabolismus und die Elimination beim Kind betrachtet und eine Bewertung der Exposition im Vergleich zu bei Kindern üblichen Nahrungsmitteln vorgenommen. Im Ergebnis wird festgestellt, dass bei empfohlener Dosierung kein Risiko durch die Einnahme Ethanol-haltiger pflanzlicher Arzneimittel besteht. Es wurden auch keine Berichte der Vergiftungszentralen über Intoxikationen mit pflanzlichen Arzneimitteln publiziert.

Introduction

Since DAB 6 (1926) (Deutsches Arzneibuch), liquid herbal medicinal products predominantly consist of liquid extracts or tinctures, representing the active substances. Their production is described in the general monograph "extracts" and their quality in details in so-called "individual monographs" of the European Pharmacopoeia. In general, these herbal preparations are produced with ethanol or mixtures of ethanol and water. These extraction solvents are also present in the final preparation and are part of the active substance of the herbal medicinal product. Examples for such extracts are liquid extracts of thyme, ivy, primrose and tinctures of valerian, chamomile, pelargonium representing the active substance of many herbal medicinal products of well-established medicinal or traditional use.

The use of ethanol or mixtures of ethanol and water is justified due to e.g. the following pharmaceutical advantages:

1. Ethanol is miscible in all proportions with water (Brand 1996).
2. Ethanol-water mixtures of 30 to 70 % are able to extract a wide range of hydrophilic and lipophilic constituents of herbal drugs.
3. They inactivate plant enzymes and thus may minimise transformation of constituents of the herbal drug.
4. They may have good antimicrobial properties depending on their ethanol concentration.

Nowadays alcohol (better: ethanol)-containing herbal medicinal products are often regarded as problematic, unpopular or controversial, especially when they are used in children. Such an extreme objection against the use of eth-

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anol in children may be caused by unjustified extrapolation of the known risks of alcohol embryopathy due to intrauterine exposure to alcohol and by the increasing number of reports on binge drinking and alcohol intoxication in elder children. But is this relevant for the ethanol exposure by herbal medicinal products?

This publication shall clarify the toxicological impact of ethanol in herbal medicinal products on the basis of scientific evidence.

Risks of ethanol overdose in children

At higher doses, ethanol is a central depressant drug that dose-dependently can induce all stages of anaesthesia. If blood ethanol concentration exceeds 2 ‰, coma and hypoglycaemia occur, sometimes with convulsions and hypokaliaemia. In severe intoxications (3–4 ‰ blood ethanol concentration), central depression with hypothermia, hypoxia, depression of breathing and even cerebral oedema can occur (von Mühlendahl et al. 1995). Blood concentrations of 1.5–2 ‰ ethanol can be observed after the intake of 1.3–1.8 g ethanol/kg b.w., corresponding to 26-36 g pure ethanol in a child of 20 kg b.w.

Inspite of these effects, ethanol is used as an antidote in cases of methanol as well as ethylene glycol intoxication because these types of alcohols are more toxic than ethanol. As an initial dose, 0.6 g ethanol/kg b.w. is given and the treatment is continued with 0.1 g/kg b.w. intravenously in a 5–10 % solution every hour (von Mühlendahl et al. 1995).

Ethanol intoxication

The rate of ethanol-intoxicated children and adolescents remarkably rose from 1998 to 2004 in Germany, Austria and Switzerland. E.g., at the university children hospital of Leipzig, the average age was 14.5 years, the mean alcohol concentration was 1.77 ‰. The average ethanol consumption amounted to 14.7 standard drinks (Schöberl et al. 2008).

Between 2002 and 2006, the Finnish main university hospital listed poisonings in 369 paediatric patients of less than 16 years, 45 % of these were children under 5 years. Ethanol was the responsible agent in 30.9 %, but only a small number of ethanol intoxications (0.6 %) was observed in children under 5 years of age, none in children between 5 and 9 years, whereas 64 % of all intoxications in children between 10 and 15 years were induced by ethanol (Kivistö et al. 2008).

That means that indeed accidental ethanol intoxication in small children is very rare, by far most intoxications in children are caused by binge drinking.

The ingestion of ethanol-containing products such as cologne, perfume and after-shave by children of less than six years is common, but serious poisoning is very rare. The risk of a serious accidental ethanol poisoning in children depends on the ethanol content of the product *and* on the amount consumed, the latter being dependent on the taste of the product. It may be assumed in general that products with a significant lower alcohol content represent a much smaller poisoning hazard. Mouthwashes, however, are a relatively frequent cause of severe intoxications in children, presumably because the taste of mouthwashes is comparable to the palatable nature of wine and liquor. Thus children are more tempted to drink large quantities (Hornfeldt 1992).

In 1994, American poison control centres listed 2937 calls related to ethanol-containing mouth rinses, an estimated incidence of 168 reports per 100.000 children younger than 6 years of age. A 15 kg child ingested 57 ml ethanol with 212 ml of a mouthwash (26.9 % ethanol), a potentially lethal dose (Shulman JD, Wells LM 1997).

The incidence of overingestion of mouthwashes by children of less than 6 years in US rose from 12.7 per 100.000 in 1991 to 20.7 per 100.000 in 1996. This increase was terminated as a consequence of the adoption of the Consumer Product Safety Commission rule requiring child-resistant packages for mouthwashes containing at least 3 g ethanol per package (Massey and Shulman 2006).

In contrast to mouthwashes, the taste of liquid herbal medicinal products is mostly unpalatable for children and thus represents a protection against accidental overingestion. Additionally, for all medicinal products containing ethanol, child-resistant packages and/or closure systems with droppers are used.

Metabolism of ethanol in children

As a further aspect the higher sensitivity of children against ethanol is frequently discussed which is regarded as a consequence of a reduced ethanol metabolism. Ethanol is metabolised almost completely (90–98 %). Elimination by urinary excretion or pulmonary exhalation is minimal. Ethanol is metabolised first to acetaldehyde and then to acetate with alcohol dehydrogenase playing the major role. This oxidation of ethanol is relatively independent of the blood concentration and is constant with time (capacity-limited elimination). Adults metabolise ethanol at a rate of about 7–10 g/h. On average about 10 ml ethanol are oxidised by a 70 kg person per hour (or about 120 mg/kg per hour) (Goodman and Gilman´s 2001). Metabolic rates are higher for chronic alcoholics and for children (Hayes 2001).

In a retrospective study between 1969 and 1984, 27 children with documented ethanol intoxication were included. The rate of ethanol elimination was greater than 6.2 mM/L/h (28.4 mg/dl/h), approximately twice the rate found in adults (15 mg/dl/h) (Leung 1986).

Ethanol content in herbal medicinal products and ethanol intake with herbal medicinal products for children

The ethanol concentrations in most liquid herbal medicinal products are between 10 % and 70 % (see Table 1). These values seem to be high when regarded as absolute figures. However, two factors have to be taken into account: On the one hand the therapeutic doses are typically very low. Characteristic doses for children of one year of age, e.g. 0.5 ml of a 12 % ethanolic solution, contain 50 µg ethanol. According to the Widmark formula (Widmark 1932), which allows the estimation of maximal blood ethanol concentrations under worst case assumptions, this dose results in blood ethanol concentrations of 0.003 to 0.008 ‰. This amount of ethanol is completely eliminated from the blood within 1–2 minutes (see Table 2).

To give another example for the maximum ethanol load by herbal medicinal products in small children: With a dose of 0.3 ml (6 drops) of a 30 % ethanolic solution, as used in children up to 3 months, 70 µg of ethanol are administered, which are eliminated within 6-7 minutes. By these 0.3 ml, a maximum blood ethanol concentration of 0.031 ‰ can be achieved (see Table 2). This is still in the range of the physiological equilibrium blood ethanol concentration of up to 0.03 ‰. As herbal medicinal products mostly are administered 3 times daily, an accumulation with enhanced blood ethanol concentrations does not occur even in such young children. In older children like in adults, blood ethanol levels resulting from the use of herbal medicinal products are even lower and the ethanol is eliminated within minutes or even seconds (Table 2).

However, there might still be concerns that ethanol, even in these low doses, could bear a risk because this substance is otherwise not consumed by young children of one year or below. In fact, drinks commonly accepted as safe and healthy even for small children contain certain amounts of ethanol. As pointed out below (Table 3), apple or orange juice typically have an ethanol content of 0.4 %, resulting in an uptake of 320 µg ethanol with only 100 ml of juice. This ethanol dose is 5- or more fold higher than the ethanol doses ingested with herbal medicinal products as mentioned above.

Additional concerns about the ethanol concentrations in these herbal medicinal products might be raised because they might lead to a habituation to the taste of ethanol or lead to local irritations in children. However, such effects are prevented by the dosing instructions, which according to the SPC (Summary of Product Characteristics) recommend a dilution of the herbal medicinal product with water or tea before consumption. Thus, in a final volume of 50 ml, the ethanol concentration amounts to 0.2-0.5 % which is in the range of or even below that of fruit juices. Therefore, neither the taste nor the pharmacological properties of these solutions are significantly influenced by the ethanol content, but rather by the phytochemical composition of the extract.

The third example in Tables 1 and 2, a valerian tincture with 66 % (V/V) ethanol**,** which is applied in a single dose of 2.5 ml, does not alter the general conclusions. The use of this herbal medicinal product is limited to patients aged 12 years or above. With this dose of 2.5 ml, 1.4 g ethanol is ingested, an ethanol quantity which corresponds to 350 ml fruit juice. For the consumption of such a volume of fruit juice there are no health concerns for children or adolescents of that age. Furthermore the herbal medicinal product has to be diluted according to the instructions for use and thus does not lead to local irritations.

As a further concern the accidental consumption of large quantities of these herbal medicinal products by children might be regarded as a risk. Such a risk, however, seems to be very unlikely. As a safety measure, droppers are used which cover the bottles of these herbal medicinal products, thus making it difficult for children to drink directly from these bottles and to draw toxicologically relevant amounts within a relevant period of time.

Furthermore, the ethanol content of these herbal medicinal products is often lower (12–30 %) as compared to freely available alcoholic beverages such as liqueurs. The taste of herbal medicinal products is typically unpleasant especially for children, which prevents the accidental consumption of larger amounts and makes a misuse unattractive. Finally, all medicines containing ethanol are labelled with “store out of the reach of children”, in contrast to alcoholic beverages lacking such labelling.

These facts lead to the conclusion that the risk of poisoning by ethanol-containing medicines is negligible. This is underlined by observations of toxicological centres which report large numbers of ethanol intoxications in children, but not with herbal medicinal products (Lockemann and Püschel 1996).

In the following the ethanol exposition by nutritional sources will be discussed in order to assess the relative risk of the different ethanol sources.

Table 1: Ethanol content and doses applied with popular herbal medicinal products.

Ethanol content of product	Age group	Single dose			Equivalent dose of apple juice [ml][1)]
		Drops	[ml]	Ethanol [g]	
12 %	Adult	30	1.1	0.11	34
	13 years[2)]	30	1.1	0.11	33
	6–12 years	20	0.8	0.07	23
	1–5 years	10	0.4	0.04	11
30 %	Adult	20	1.0	0.24	75
	13 years[2)]	20	1.0	0.24	75
	6–12 years	15	0.8	0.18	56
	1–5 years	10	0.5	0.12	38
	3 months to 1 year	8	0.4	0.10	30
	< 3 months	6	0.3	0.07	23
66 %	Adult	–	2.5	1.40	438
	13 years[2)]	–	2.5	1.40	438

[1)] With 0.4 % ethanol content. [2)] 13 years is the youngest age for which the adult dose applies.

Table 2: Blood ethanol concentrations and elimination times after single doses of herbal medicinal products.

Ethanol content of product	Age group	Body weight [kg]	Maximum blood ethanol content [‰][1)]	Elimination time [min]
12 %	Adult	70	0.003	1
	13 years[2)]	39	0.005	2
	6–12 years	20	0.008	1
	1–5 years	10	0.008	1
30 %	Adult	70	0.006	2
	13 years[2)]	39	0.010	4
	6–12 years	20	0.015	3
	1–5 years	15	0.014	2
	3 months to 1 year	6	0.029	5
	< 3 months	4	0.031	6
66 %	Adult	70	0.033	13
	13 years[2)]	39	0.061	23

[1)] Widmark 1932. [2)] 13 years is the youngest age for which the adult dose applies.
Blood ethanol content was calculated according to the Widmark formula (Widmark 1932) under worst-case assumptions. Calculation of elimination rates was based on an elimination rate of 0.09 $g \cdot kg^{-1} \cdot h^{-1}$ (adults) and 0.20 $g \cdot kg^{-1} \cdot h^{-1}$ (age < 13 years) (Lammninpää 1995; Goodman and Gilman´s 2001).

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Table 3: Ethanol uptake with usual doses or servings of food and beverages.

Product (ethanol content)[1)]	Age group	Dose or serving	Ethanol content [g]
Apple juice (0.4 %)	Adult	200.0	0.64
	12 years	200.0	0.64
	1 year	100.0	0.32
Rye bread (0.3 %)	Adult	50.0	0.12
	12 years	50.0	0.12
	1 year	25.0	0.06
Kefir (1 %)	Adult	500.0	4.00
	12 years	200.0	1.60
	1 year	100.0	0.80
Banana (0.3 %)	Adult	200.0	0.48
	12 years	200.0	0.48
	1 year	50.0	0.12
Beer (5 %)	Adult	300.0	12.00
	16 years	300.0	12.00

[1)] Honma et al. 1985; Wucherpfennig 1982; Anon. 1999; Kiesewetter 1996, Senser et al. 2003.

Table 4: Blood ethanol concentrations and elimination after consumption of food and beverages.

Product (ethanol content)[1)]	Age group	Dose [g]	Maximum blood ethanol content [‰][2)]	Elimination time [min][3)]
Apple juice (0.4 %), 0.2 l	Adult	200	0.015	6
	12 years	200	0.028	11
	1 year	100	0.055	10
Rye bread (0.3 %),	Adult	50	0.003	1
	12 years	50	0.005	2
	1 year	25	0.010	2
Banana (0,3 %)	Adult	200	0.019	38
	12 years	200	0.035	28
	1 year	50	0.069	25
Kefir (1 %)	Adult	500	0.095	38
	12 years	200	0.069	28
	1 year	100	0.137	25
Beer (5 %)	Adult	300	0.286	114
	16 years	200	0.367	147

[1)] See Table 3. [2)] Widmark 1932. [3)] See Table 2.

Ethanol intake with foodstuff and drinks

The human body produces physiological blood levels of ethanol of up to 0.03 ‰. Additionally, many foodstuffs are exogenous sources of ethanol, e.g. fruits, in which ethanol is produced from carbohydrates (see Table 3). The blood ethanol concentrations obtained by different amounts of these foodstuffs are shown in Table 4.

E.g. bananas, ten days after purchase, contain 6 g ethanol/kg. Other fruits as well as fruit juices contain ethanol, too: in fruit juices up to 4 g/L, in grape juice up to 10 g/L are found.

One kilogram bread contains 2-4 g ethanol, kefir as well as sauerkraut contain 5 g/kg.

A 30 kg person, drinking 0.2 L apple juice, ingests 0,64 g ethanol resulting in an ethanol blood level of 0.036 ‰, drinking 0.25 L kefir, resulting in a blood level of 0.111 ‰.

Conclusion

Without doubt, the intake of considerable amounts of ethanol by children represents a risk. However, in all assessments the dose is the decisive factor for the relevance of the risk. As nowhere a health risk by intake of e.g. apple juice or kefir is discussed, the risk of ethanol-containing herbal medicinal products is negligible when used at the recommended dose.

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