



# AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

## Ethanol in Liquid Preparations Intended for Children

Ethanol is present in more than 700 pharmaceutical liquid preparations, ostensibly as an "inert" solvent or diluent.<sup>1</sup> Despite recent voluntary efforts by several pharmaceutical companies to replace alcohol or reduce its content, there remain on the market an excessive number of liquid medications containing alcohol in concentrations ranging from 0.3% to 68%, eg, teething preparations, decongestants, and cough medicines. The presence of ethanol in children's medication is of major toxicologic interest with respect to both acute ingestion and passive exposure that occurs during therapy with ethanol-containing products. This commentary focuses upon the toxicology of ethanol in children and the determination of acceptable alcohol concentrations in children's medication.

### INTERACTION WITH OTHER DRUGS

When taken in conjunction with other drugs, medicines containing alcohol may produce undesirable interactions. Acute ethanol administration may alter drug absorption<sup>2</sup> or impair the degradation of other drugs.<sup>3</sup> When taken with sedating drugs, it may result in enhanced psychomotor impairment.<sup>4,5</sup> Chronic ethanol administration, which induces drug-metabolizing enzymes (such as P-450), may be of clinical importance by altering the clearance of several drugs (phenobarbital, phenytoin, meprobamate, and warfarin).<sup>3</sup> Disulfiram (Antabuse) reactions, symptoms of which include flushing, tachycardia, nausea, vomiting, and, in severe forms, cardiac arrhythmias, cardiovascular collapse, respiratory depression, and convulsions, may also be induced by alcohol-containing medicines. Of more direct importance to pediatricians are recent reports of disulfiram-like reactions that occur in some individuals after the simultaneous use of an-

tibacterial drugs such as moxalactam, metronidazole, sulfonamides, chloramphenicol or cefamandole, and alcoholic beverages or medicinal elixirs.<sup>6-9</sup>

### ESTABLISHING CRITERIA FOR ALCOHOL CONTENT IN CHILDREN'S MEDICATION

#### Toxicokinetics of Alcohol

The effects of acute and chronic alcohol ingestion in adult populations have been described previously.<sup>10-12</sup> However, except in cases of acute poisoning,<sup>13-17</sup> little information is available on the effects of ethanol in the pediatric age group. Furthermore, interpretation of the data is also made difficult by the conflicting information on ethanol kinetics in children. For example, despite reports that alcohol dehydrogenase activity does not reach adult levels until 5 years of age,<sup>18</sup> pharmacologic studies in acutely intoxicated children show that clearance of ethanol is more rapid than that reported in adults.<sup>16</sup> In addition, the precise blood ethanol concentrations that produce CNS symptomatology or death in children remain controversial.<sup>19,20</sup> Although the reported lethal dose of ethanol is 5 to 8 g/kg in adults and 3 g/kg in children,<sup>19</sup> morbidity and mortality may occur with lower amounts secondary to induced hypoglycemia<sup>13-16</sup> or interaction with other drugs.<sup>2-5,7-9</sup>

The major acute toxic effect of ethanol is neuronal dysfunction. CNS effects, including decreased reaction time, muscular incoordination, behavioral changes, etc are usually present with blood ethanol concentrations of approximately 100 mg/100 mL, but have been reported with concentrations as low as mg/100 mL.<sup>21</sup> Based upon these data, we have arbitrarily established 25 mg/100 mL as a blood ethanol concentration not to be exceeded following a single dose of alcohol-containing medication. The blood ethanol concentration (BEC) in children following ingestion can be projected using available

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pharmacokinetic data.<sup>19,22</sup> For our calculations (Table 1) we have utilized the pharmacokinetic formula:

$$\text{Plasma concentration } (C_p) = \frac{\text{Dose } (D)}{\text{Volume distribution } (V_d)}$$

to estimate the dose of ethanol that would be necessary to produce a maximum blood ethanol concentration of 25 mg/100 mL. In reality, the measured blood ethanol concentration would be predicted to be lower than our projected values because these are based on the assumption that the entire dose is completely and instantaneously absorbed, the volume of distribution is constant, and no degradation has taken place.

Additionally, in the pediatric population, it is unclear whether the BEC is affected by chronic alcohol ingestion. Based upon computer simulation studies for children between 6 and 12 years of age, the ingestion of alcohol every four hours in concentrations of 10% or less would not result in accumulation of blood ethanol (W. Schary, personal communication, 1982). Hence, in the sample problem in Table 1, the 6-year-old child would need to ingest 40 mL of 10% ethanol every four hours in order to maintain a BEC of 25 mg/100 mL.

### Volume Permissible in Ethanol-Containing Products

The total amount of ethanol present in each container is also of concern, since possible toxic or lethal blood ethanol concentrations might be produced in small children after accidental ingestion of the entire contents. Utilizing the lethal *Poisindex* value of 3 g/kg, the ingestion volume necessary to produce the potential lethal blood level in children can be calculated (Table 2). These extrapolated levels do not, however, take into consideration problems induced by hypoglycemia or drug interactions.

### Packaging Recommendations

It is desirable that no ethanol be included in medicinal products intended for use in children. However, if ethanol is required to solubilize the active ingredients, the Committee on Drugs has made the following specific recommendations to the FDA: (1) Over-the-counter (OTC) liquid preparations should be limited to a maximum of 5% v/v ethanol. (2) Physician supervision is suggested for children less than age 6 years using OTC preparations containing alcohol. (3) The amount of ethanol contained in any medicinal preparation should not be able to produce a blood concentration greater than 25 mg/100 mL after a single recom-

**TABLE 1.** Volume (Milliliters) of Ethanol Preparation Predicted to Produce a Blood Ethanol Concentration of 25 mg/100 mL\*

% Ethanol (v/v) in Product	Age (Weight)					
	2 yr (12 kg)	4 yr (16 kg)	6 yr (21 kg)	8 yr (27 kg)	10 yr (32 kg)	12 yr (38 kg)
2.5	91	122	160	205	243	289
5.0	46	61	80	103	122	144
7.5	30	41	53	68	81	96
10.0	23	30	40	51	61	72
12.5	18	24	32	41	49	58
20.0	11	15	20	26	30	36
25.0	9	12	16	21	24	29

\* Values were calculated from data contained in McCoy et al,<sup>23</sup> by use of the formula: dose (in milligrams) = plasma concentration ( $C_p$ ) times volume distribution ( $V_d$ ) and assuming that absorption is complete. For example, the calculation to obtain the value of 40 mL for a 6-year-old ingesting a product containing 10% alcohol would be made as follows:  $C_p = 250 \text{ mg/L}$  and  $V_d = 0.6 \text{ L/kg} \times 21 \text{ kg}$ ; therefore, dose =  $250 \text{ mg/L} \times (0.6 \text{ L/kg} \times 21 \text{ kg}) = 3,150 \text{ mg}$ . Because for absolute ethanol (specific gravity 0.789),  $1 \text{ g} = 1.27 \text{ mL}$ ,  $31.5 \text{ g} = 4 \text{ mL}$ ; thus, for 10% ethanol, the calculated volume is 40 mL.

**TABLE 2.** Volume (Milliliters) of Ethanol Preparation Predicted to Produce a Potential Lethal Dose\*

% Ethanol (v/v) in Product	Age (Weight)					
	2 yr (12 kg)	4 yr (16 kg)	6 yr (21 kg)	8 yr (27 kg)	10 yr (32 kg)	12 yr (38 kg)
2.5	1,824	2,432	3,192	4,104	4,864	5,776
5.0	912	1,216	1,596	2,052	2,432	2,888
7.5	608	811	1,064	1,368	1,621	1,925
10.0	456	608	798	1,026	1,216	1,444
12.5	365	486	638	821	973	1,155
15.0	304	405	532	684	811	963
20.0	228	304	399	513	608	722
25.0	182	243	319	410	486	578

\* Values are calculated based on a lethal dose of 3 g/kg (3.8 mL/kg) (*Poisindex*). For example, a 6 year old (21 kg) ingesting a 10% ethanol product:  $3.8 \text{ mL/kg} \times 21 \text{ kg} = 79.8 \text{ mL}$  of absolute ethanol; for a 10% solution the calculated volume =  $79.8/0.1 = 798 \text{ mL}$ .

mended dose. (4) Appropriate intervals between medication doses should be prescribed to prevent the accumulation of blood alcohol. (5) The packaged volume of ethanol-containing products should be kept to a reasonable minimum to prevent potential lethal ingestions. (6) Safety closures should be recommended for medications with greater than a 5% ethanol content.

### CONCLUSIONS

Pediatricians and other health care providers should be aware of the widespread presence of

alcohol in liquid medications and its potential toxicity. Alcohol-containing medicines may affect the disposition of other drugs, cause undesirable drug interactions, or induce disulfiram (Antabuse)-like reactions. Since CNS toxicity occurs when the concentration of ethanol in the blood is 25 mg/100 mL, a single dose of alcohol-containing medication must not be able to produce this level of ethanol. Although fatal blood ethanol concentrations are widely quoted, including those in Table 2, such information does not take into consideration the effects of chronic administration, effects of simultaneous treatment with other medications, possible development of hypoglycemia, and reported fatalities with lower blood concentrations. Finally, continued efforts should be made to have alcohol removed from liquid preparations for children. In those instances in which alcohol is a necessary solvent, preparations should be packaged in small volumes with safety closures.

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