TAB A

United **States**
CONSUMER **P**RODUCT **S**AFETY COMMISSION
Washington, D.C. 2020'7

MEMORANDUM

DATE: November 14, 1997

To   **:**   Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Epidemiology and Health Sciences

Through :   Marilyn L. Wind, Ph.D., Division Director, Health Sciences Division *M&W*

From   **:**   Val H. **Schaeffer,** Ph.D., Pharmacologist, Health Sciences Division. *V.S.*

**Subject :**   Toxicity Assessment of Topical Minoxidil

Introduction

Topical minoxidil is a liquid medication that can be applied to the scalp to stimulate hair regrowth in men and women with androgenetic alopecia. Androgenetic alopecia is the common pattern of hair loss resulting **from** genetic and hormonal factors. It is expressed as localized baldness of the vertex of the scalp in males and as thinning hair along the top of the scalp in females. The Food and Drug Administration (FDA) approved the sale of topical minoxidil as an over-the-counter (OTC) product available to consumers without a prescription in February 1996. Minoxidil also is a potent vasodilator which effects vascular and cardiac function, if ingested. It is available by prescription in tablet form for treatment of severe hypertension. The oral prescription form of minoxidil automatically requires special packaging under the Poison Prevention Packaging Act **(PPPA).** The PPPA does not require special packaging for the topical form of minoxidil, although some companies **voluntarily** comply with the regulation. The increase in consumer access to minoxidil as a result of OTC status combined with its potential as a serious ingestion hazard to young children has led the U.S. Consumer Product Safety Commission (CPSC) staff to examine topical minoxidil as a candidate for special packaging requirements under the PPPA.

This assessment provides the necessary toxicity information on topical minoxidil to characterize the ingestion hazard and establish a regulated level above which exists a reasonable risk of serious injury to young children. Information on chemistry/formulation, **absorption/pharmacokinetics/metabolism,** pharmacologic/therapeutic action, toxicity, and poisonings are reviewed and evaluated. **The** assessment concludes that ingestion. of small quantities (less than a teaspoon) of topical minoxidil by a child under five years of age may cause serious injury as interpreted for the purposes of complying with the PPPA.

Chemistry and Available Formulations

Minoxidil occurs as a crystalline solid known as **2,4-diamino-6-**piperidino-3-oxide with the chemical structure depicted in the figure at the right. It is soluble in water and alcohol and is formulated for hair regrowth at a two percent solution in 60 percent alcohol v/v, propylene glycol, and water (Physicians Desk Reference, 1996). The concentration is 20 milligrams (mg) of minoxidil per milliliter (ml) of solution. The topical formulation has been available by prescription since 1988 prior to its approval as an OTC preparation.
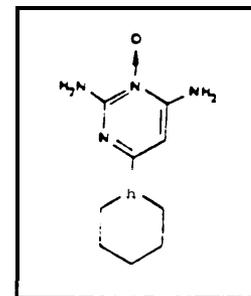
Use instructions direct that one ml (20 mg) be applied to the desired area of the scalp twice daily. At least **four** months of daily application is generally required before there is evidence of hair growth. The degree and onset of hair growth is variable among individuals. Continuous application is necessary to maintain continued hair regrowth. The predominant package size is 60 ml in volume which lasts about 30 days if used as directed.

A five percent minoxidil solution has very recently been approved by the FDA as an OTC product. In addition, research has been conducted on preparations that combine minoxidil with agents that enhance dermal penetration or stimulate the growth of hair follicles **(Saton** and **Atton,** 1993). These have not been approved for commercial use at this time.

The tablet form of minoxidil is prescribed for use as an antihypertensive drug. It is particularly effective at lowering blood pressure in severe hypertensives who are resistant to other less potent drugs. Minoxidil tablets are typically used in combination with a β-adrenergic blocking agent and a diuretic to maximize its effect on blood pressure while minimizing 'associated side effects (see section on **pharmacologic** effects). Minoxidil is available as 2.5 mg, 5 mg, and 10 mg tablets. The effective dosage is usually between 0.2 to 1 mg/kg/day (roughly 5 to 40 mg/day for an adult) depending on the individual and the desired antihypertensive response. Use in children has been limited with a similar effective body weight-normalized dose range as adults (0.2 to 1 mg/kg/day). Because of possible adverse effects, the maximum recommended daily therapeutic dosage is 100 mg in adults and 50 mg for children under the age of 12.

Pharmacokinetics and Metabolism

Greater than 95 percent of orally ingested minoxidil (tested as a solid or liquid) is rapidly absorbed through the gastrointestinal tract within 30 to 60 minutes (Lowenthal and **Affrime,** 1980). The drug distributes to vascular and extravascular sites. The plasma half-life of minoxidil and its metabolites is 3 to 4 hours. It is retained longer in arterial smooth muscle, the major site of pharmacologic action.

Minoxidil is extensively metabolized in the liver primarily to a glucuronide at the N-oxide moiety. This portion of the molecule can also undergo sulfation or reduction. Some

hydroxylation of the piperidinyl group also occurs. Elimination of minoxidil and its metabolites from the body occurs almost entirely by renal excretion. About 80 percent of minoxidil absorbed by the oral route is recovered in the urine within 24 hours (Gottlieb et al., 1972). Urinary excretion is complete by four days following ingestion of a single dose. Most major metabolites of minoxidil are not as pharmacologically effective as the parent compound. However, minoxidil*[N-O]*sulfate has been shown to have vasodilator activity when administered to experimental animals and humans (Johnson et al., 1983).

Absorption of topical minoxidil from the scalp is low (Franz, 1985). Systemic bioavailability from the recommended topical application to undamaged skin ranges from 0.3 to 4.2 percent (average of about 1.4 percent). The cumulative and average serum minoxidil concentrations following a daily recommended topical application of two percent minoxidil range from 5 to 20 percent of that resulting from the lowest effective oral therapeutic dose of minoxidil (Kakowsky, 1994). Based on these comparative pharmacokinetic studies, the FDA concluded that there was an adequate margin of safety between the systemic dose achieved as a result of the recommended topical application and the minimum systemic dose required to cause vasodilation in hypertensives (Lipinsky, 1994).

Increase in the dose applied or the frequency of application will increase the amount of minoxidil absorbed through the skin (Eller et al., 1989). However, maximum absorption is limited by the rate at which minoxidil penetrates the stratum comeum (outer layer of the skin). Factors that alter the integrity of the stratum comeum, such as inflamed or damaged skin and co-administration of agents that enhance permeability, can increase the systemic bioavailability of minoxidil.

Health Effects From Ingestion of Pharmacologic Doses of Minoxidil

There have been several medical reviews of the pharmacologic action and associated effects from therapeutic ingestion of minoxidil, particularly in hypertensive adult populations (Kosman, 1980; Miller and Love, 1980; Linas and Nies, 198 1). The most prominent effects are hemodynamic changes that result in sustained tachycardia (increased heart rate), increased cardiac output, and decreased blood pressure. Less frequent effects with significant adverse health consequences include salt and fluid retention and edema, aggravation of angina, and pericardial effision in patients with renal impairment. Repeated ingestion over several months can produce hypertrichosis (overstimulated hair growth) particularly to the face and to a lesser extent to the limbs and scalp. Less severe symptoms of nausea, headache, fatigue, and dermatologic reactions have been occasionally reported.

Hemodynamic Effects

Oral ingestion of small amounts of minoxidil causes vasodilation through direct action on the arteriolar smooth muscle. For this reason, it is approved as a potent anti-hypertensive drug for individuals with high blood pressure. Although minoxidil lowers total vascular resistance, several physiological adaptive responses do occur subsequent to the

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vasodilation that can counteract its therapeutic action. The decrease in mean arterial pressure caused by minoxidil leads to a reflex activation of the adrenergic nervous system'. The result is an increase in heart rate, cardiac contractility, and cardiac output. The increased cardiac output opposes the antihypertensive effect from the primary vasodilation. The effects on the heart secondary to adrenergic stimulation can be blocked by co-administration of a β-adrenergic blocking agent, usually propanolol.

Several clinical studies have established that the minoxidil/β-blocker regime is an effective means of lowering blood pressure and managing hypertension, particularly in those unresponsive to more conventional antihypertensive drugs. The effective minoxidil dose range of 0.2 to 1.0 mg/kg/day reduces systolic and diastolic blood pressures of individuals with moderate or severe hypertension by more than 20 mm Hg (Gilmore et al., 1.970; Hall et al., 1979) The anti-hypertensive effect begins within 30 to 60 minutes after administration of a single dose and slowly declines over 12 to 72 hours, well after serum levels have peaked and substantially declined (Shen et al., 1975) reason, blood minoxidil levels are not always a reliable indicator of pharmacologic effect. While a single pharmacologic dose of minoxidil will produce an antihypertensive response, repeated administration for three to seven days (depending on the dose) is usually required to achieve the maximum effect. Dose-response relationships suggest that mirroxidil is less effective in reducing blood pressure of normotensive and mildly hypertensive individuals than severe hypertensives. Hypertensive children do not appear to differ substantially from adults in terms of their blood pressure response to minoxidil provided the dose is appropriately adjusted for the different body weights (Pennisi et al., 1977).

The hemodynamic response to minoxidil administered in the presence and absence of a P-blocker is somewhat different. Minoxidil alone is not as effective in reducing mean arterial pressure in hypertensive patients as when administered in combination with a β-blocker (Zin and Martin, 1979). As expected, minoxidil in the absence of a P-blocker can result in significant increases in heart rate and cardiac output. In controlled studies, typical therapeutic doses of minoxidil raise the heart rate by an average of 10 to 20 beats per minute. This response can be sustained for several days following a single dose (Hall et al. 1979).

Salt and Fluid Retention

Adrenergic stimulation secondary to minoxidil-induced vasodilation increases plasma renin leading to the formation of angiotensin II. Production of angiotensin II causes retention of sodium and water by the kidney and an increase in blood volume which can work against the desired anti-hypertensive action. Uncontrolled salt and fluid retention can lead to local or generalized edema and is especially problematic in patients with renal impairment (Mutterperl et al., 1976) to prevent fluid retention and its consequences, a diuretic, such as furosemide, is usually administered to hypertensives undergoing minoxidil therapy.

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[1] The adrenergic nervous system is a collection of nerve fibers that, when stimulated, secrete substances that increase heart rate, cardiac output, and dilate the airways.

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Cardiac Complications

Oral minoxidil therapy can precipitate angina attacks in patients with unstable angina (Campese et al., 1979) This may be a consequence of the added demands for oxygen from reflex cardiac stimulation and/or reduced coronary perfusion. It can usually be controlled with an adequate dose of a P-blocking agent.

Pericardial effusion has been. documented in about three percent of patients on minoxidil therapy (Wilburn et al., 1975). It is most common in patients with severe renal impairment and is thought to be a consequence of uncontrolled fluid retention.

Minoxidil ingestion frequently results in electrocardiographic (ECG) changes (Hall et al., 1979). The ECG abnormalities generally appear after the first few doses, but disappear upon long term therapy or discontinued use. The evidence does not indicate an association with cardiac damage and the ECG changes are not considered adverse.

Health Effects From Overdose Ingestions of Minoxidil

Information on adverse health effects from accidental and intentional ingestions of minoxidil was retrieved from several sources. These consist of published reports in the medical literature, data from the American Association of Poison Control Centers (AAPCC), data from the FDA Spontaneous Reporting System (SRS), and reports from the injury surveillance databases maintained by CPSC. The poisoning information from these various sources is summarized in the table below. Although not numerous, some serious injuries from minoxidil overdose have been reported. They usually result from intentional ingestions in adults and often involve co-ingestions of other substances. Reports of serious injury following accidental ingestion in children are fewer. Incidents involving both m.inoxidil tablets and topical solution have contributed to the serious poisonings. As expected, the most commonly cited injuries are prolonged1 hypotension and tachycardia that require hospitalization, hemodynamic monitoring and sometimes intravenous (IV) treatment with a vasopressor. Reports of two deaths associated with minoxidil overdose were retrieved from this search.

Data Source	Reporting Dates	Minoxidil Formulation	Population	Incidents	Adverse Outcome[a]	Deaths
AAPCC	1985-1991	tablet+liquid	adults+child.	285	16	1 adult
	1995	liquid	children<6 yr	4		
FDA/SRS	1983-1997	liquid	adults+child.	264"	1 adult 1 child	1 adult
CPSC	1995	liquid	child<6 yr	1		
Published Reports	1980-1993	tablet	adults	1	1	-
			children<6 yr	2	2	
		liquid .	adults	2	2	

[a] significant adverse outcomes associated with ingestion

[b] incidents involving either dermal application or ingestion that were associated with overdose

AAPCC Data

-The AAPCC collects reports, of toxic exposures to drugs, household products, etc. made to participating poison control centers in the United States. The Department of Emergency Medicine at the Carolina Medical Center in collaboration with the Carolina Poisons Center evaluated AAPCC records of all minoxidil exposures from 1985 through 1991 (Rose and Tomaszewski, 1993). There were 285 incidents reported to AAPCC in this time period. About half (5 1%) of the incidents occurred in children under six years of age. The study did not distinguish between ingestions of minoxidil tablets and topical solution. The amounts of minoxidil ingested were not recorded. Most incidents were accidental ingestions (80%) and some involved co-ingestions (21%) of other substances. Just under half (46%) of the cases *were* referred to a health care facility but only 11 percent resulted in admissions. Sixteen incidents were reported to develop moderate/severe toxicity with one reported death. Most of the more serious poisonings were intentional ingestions (69%) and involved co-ingestions (81%). It was not reported how many of these incidents occurred in children. The most frequently reported adverse effects were hypotension (69%), tachycardia (38%), and lethargy (3 1%) with 44 % requiring medical treatment. The one death was a suicide caused by co-ingestions of minoxidil, other vasodilators, and acetaminophen.

The AAPCC compiles its poisoning data into a toxic exposure surveillance system (TESS) database (Litovitz et al., 1997). CPSC has purchased annual TESS data on pediatric exposures in children under five years of age since the late 1980s. Four accidental ingestions of topical minoxidil liquid by children under five years of age were reported in 'TESS in 1995. This increased to 43 reported cases in 1996. One case in 1996 exhibited moderate

toxicity. The other TESS cases in 1995 and 1996 were not reported to cause more than minimal toxic effects. Exposures involving minoxidil tablets are coded in a category that includes "other vasodilators". Therefore, it is not possible to isolate incidents specific to minoxidil tablets. There were two childhood ingestions of *"other* vasodilators" reported in 1995 that resulted in a moderate (AAPCC criteria) toxicity. Prior to 1995, topical minoxidil was not given a specific code within the database.

FDA/S" Database

The SRS is a computerized database of adverse drug events maintained by the FDA Division of Pharmacovigilance and Epidemiology. The system only contains reports that occur after marketing of the drug. The purpose is to screen for potential adverse events not detected during pre-market clinical trials. Most reports are filed by drug manufacturers who are required by law to submit any known incidents of adverse effects to the FDA. The FDA makes clear that there is no verification that the suspect drug(s) identified in SRS incidents cause the reported adverse event.

There have been 16,795 SRS reports on topical minoxidil between 1983 and March, 1997 (Goetsch, 1997). Almost all were reported to the drug manufacturer by consumers and then forwarded to FDA. A relatively small subset (264) of total incidents resulted from an overdose of the medication. The number of overdose reports have steadily climbed from less than 10 per year in 1983-1991 to around 90 in 1996. Most of the reported adverse effects were dermal reactions to excessive application of topical minoxidil to the scalp. However, FDA cited three serious SRS overdose cases from accidental or intentional ingestions of topical minoxidil which led to serious outcomes.

One case was a suicide in which an adult male ingested the contents of five bottles (6 grams in 300 ml) of topical minoxidil and died. No other details were provided. A second case was an adult male who mistakenly ingested 15-20 ml (300 - 400 mg) of topical minoxidil and experienced syncope (fainting), severe hypotension, atrial fibrillation, abnormal EKG indicating cardiac ischemia, and acute renal failure. The person was taking anti-hypertensive medication at the time of the poisoning but no other details of his prior medical condition were cited. The third case *was an accidental ingestion of topical minoxidil by a two year old child. She was found with an empty bottle that had been full earlier. She was admitted to an intensive care unit in a lethargic state with a pulse of 160 (above normal range), blood pressure of 106/60 (within normal limits), but was discharged the same day. The amount of minoxidil actually ingested was never established.

Two other childhood ingestions (separate cases) of topical minoxidil were reported in SRS to result in hospital visits. In both incidents, no adverse outcomes were recorded but the children were retained at the hospital for observation. While the children gained access to the medication in these cases, it was suspected by the hospital that no minoxidil was consumed. The FDA report concluded that a requirement for child-resistant packaging would assist in preventing accidental childhood ingestions of topical minoxidil. (Goetsch, 1997).

CPSC Databases

CPSC maintains a database of consumer product-related injuries collected from the National Electronic Injury Surveillance System (NEISS). NEISS monitors emergency room visits to a statistically-based sample of selected hospitals throughout the United States. A single childhood poisoning case associated with rninoxidil was reported in the NEISS database between 1988 to 1997. This was an accidental ingestion of an unknown quantity of topical minoxidil by a two year old male. The child was seen in an emergency room with normal temperature, puke, and respiration and was released the same day without treatment. It is not known whether the minoxidil package was secured with a child-resistant closure at the time of the incident.

CPSC also maintains the Injury and Potential Injury Incident (IPII) files of consumer product-related incidents reported through letters, telephone calls, media articles and Death Certificate files of consumer product-related deaths. There were no minoxidil-related injuries or deaths found in these databases for the 1988 to 1997 time period.

Published Reports

Citations for five published case reports of injuries following rninoxidil ingestion were found in literature searches of MEDLINE and POISINDEX ® databases.   Three of the cases were intentional ingestions of minoxidil tablets or liquid by adults. Two of the reports involved adult males, both of whom were estimated to have consumed 50-60 ml (10 - 20 mg/kg) of two percent topical minoxidil (McCormick et al., 1989; MacMillan et al., 1993). Both cases involved co-ingestion of alcohol and one case also included co-ingestion of several other substances. The clinical courses were remarkably similar. A few hours after ingestion, the individuals were brought to the hospital emergency room in a disoriented and unresponsive state. They were severely hypotensive upon arrival with moderate tachycardia. Saline and vasopressors were administered intravenously which stabilized blood pressure at below normal levels and improved patient responsiveness. Cardiac output was markedly elevated and systemic vascular resistance was reduced confirming vasodilation. Hemodynamic parameters slowly improved over the next 72 hours. Pulmonary complications occurred in both cases and ischemic ECG changes were noted in one of the cases. The authors of both publications concluded that minoxidil was primarily responsible :for the life threatening effects, and that co-ingested substances, such as alcohol, were not consumed in amounts suffkient to cause the reported symptoms. Both individuals fully recovered after being hospitalized for eight to nine days .

The other published report of adult overdose describes a suicide attempt in a woman who ingested no more than 650 mg minoxidil in tablet form, along with an unknown quantity of beer and wine (Poff and Rose, 1992). She arrived at the emergency room, 90 minutes post-ingestion, alert with mild tachycardia and normal blood pressure. She became moderately hypotensive (BP low of around 95/40 mm Hg) over the next few hours despite intravenous saline treatment and gastric lavage. Electrocardiograph (ECG) changes typically

associated with minoxidil were noted. Her hemodynamics improved over the next 24 hours and she was released 32 hours post-exposure. A total serum minoxidil of 3 140 ng/ml was measured three hours after ingestion. This is consistent with an ingestion of several hundred milligrams of minoxidil.

There is one published case report of an accidental ingestion of rninoxidil in a two year old child (Isles et al., 198 1). The child allegedly swallowed 20 tablets (5 mg each) of minoxidil (total dose of 100 mg). An ECG confirmed moderate tachycardia (160 beats per min) which gradually decreased over the 40 hour hospital stay, but no other abnormalities were observed. The patient remained alert with normal blood pressure. Although no minoxidil tablets were recovered during emesis and gastric lavage, a serum minoxidil of 150 ng/ml at three hours post-ingestion confirmed absorption of the drug. This level was about four-fold higher than that for an adult who received a single dose of 30 mg rninoxidil three hours following ingestion (Royer et al., 1977). That the vascular volume of the average two year old is about 3.5 times less than the average adult, the serum level is more consistent with an ingestion of 20 to 50 mg minoxidil than 100 mg^2. There was no minoxidil detected in the child's blood at 13 hours following ingestion.

An accidental ingestion in a three year old male who swallowed an estimated one to two milliliter of a three percent minoxidil solution (30 to 60 mg) is described in the Physicians' Desk Reference. After vomiting, the child was treated in an emergency room. He had an above average pulse (152 bleats per min) but was alert, with normal blood pressure and respiration, and no obvious signs of distress. The patient's serum total minoxidil was consistent with the estimated amount of ingestion. The child was discharged without sequelae.

Toxicity Studies in Animals

Minoxidil has been shown to cause toxicity in experimental animals administered large doses by the oral and intravenous routes. The oral and intravenous LD_{50}s for rats was 132 mg/kg and 49 mg/kg, respectively (Carlson and Feenstra, 1977). Oral minoxidil doses between 0.5 and 3 mg/kg for two consecutive days caused epicardial and subendocardial hemorrhages and necrosis in dogs (Herman et al., 1979). In a separate study, larger doses (3 to 30 mg/kg) administered for one year produced atrial hemorrhages in dogs (DeCharma et al., 1973). There is some evidence that the cardiotoxicity is a secondary effect of the minoxidil-induced vasodilation (Mesfin et al., 1995). The cardiac lesions in dogs did not

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[2] Royer et al. report a serum minoxidil of 40 ng/ml in an adult ingesting 30 mg of minoxidil. Blood volume per body weight is about 2.2 times higher in an infant than an adult. This relationship usually decreases to unity between the second and third years of age and then remains constant through adulthood. The body weight of the average adult and two year old boy are 70 kg and 13.3 kg, respectively. Given this information, the ingested minoxidil that produces a serum level of 150 ng/ml in a two year old boy can be estimated as follows: 150 ng/ml ÷ 40 ng/ml x 30 mg x 13.3 kg ÷ 70 kg = 21.4 mg of ingested minoxidil. This is a lower estimate since it assumes that the two year old boy has the same blood volume per body weight relationship as an adult. An upper estimate assuming the child has the blood volume per body weight relationship of an infant is 2.2-fold higher or 47.0 mg of ingested minoxidil.

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occur unless the heart rate increased by more than 55 beats per minute and mean arterial pressure fell at least 30 mm Hg (Mesfin et al., 1996). Cardiotoxicity can also be produced in rats and minipigs administered higher doses of minoxidil than required in dogs (Herman et al., 1996). The cardiac lesions described in experimental animals have not been reported in humans treated with therapeutic doses of minoxidil.

The carcinogenicity, mutagenicity, and reproductive/developmental toxicity of minoxidil have also been studied in experimental animals (Physcians' Desk Reference, 1996). Female mice administered minoxidil in their diet (10, 25, and 63 mg/kg) for two years developed an increased incidence of malignant lymphomas at all dose levels. The increase was small (within the range of historical controls) and not dose-related. There was a dose-related increase in hepatic nodules (putative pre-cancerous lesion) in the male mice fed minoxidil. Minoxidil did not cause increased tumors in rats administered similar doses. There was an increased incidence of mammary adenomas and adenocarcinomas in female mice dermally administered minoxidil at 8, 25, and 80 mg/kg dose levels for two years. The tumors were attributed to increased prolactin levels. There was an increased incidence of adrenal pheochromocytomas in male and female rats following chronic dermal administration of minoxidil. Minoxidil produced mostly negative results in a battery of mutagenicity and other genotoxicity tests.

Minoxidil caused a reduction in fertility when orally administered to male and female rats at 10 mg/kg. This dose level also caused increased fetal resorption in pregnant rabbits, but not pregnant rats. Higher dose levels were required to produce maternal toxicity in these experimental animals. The carcinogenic&y and reproductive toxicities reported in experimental animals following repeated dosing of minoxidil are not considered to be relevant to the adverse health effects anticipated to occur in young children following a single acute ingestion.

Conclusions and Recommendations

In order to establish a special packaging standard under the PPPA, an ingested dose level must be determined below which children under five years of age are protected from the likelihood of serious injury or illness. The table below summarizes the expected hemodynamic effects in healthy individuals following ingestion of minoxidil. The dose ranges are presented as a milligram amount ingested by a child weighing 10 kg and as a dose normalized to body weight. The same body weight-normalized dose of minoxidil are expected to produce similar pharmacologic and toxicologic effects in adults and children. A body weight of 10 kg has been used as the reference weight for a young child in past PPPA toxicological evaluations (Inkster, 1994; Aitken, 1996).

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Dose Range		Expected Hemodynamic Effect in Healthy Individuals	Other Information
mg/kg	mg[1]		
<0.2	<2	insignificant effects	below therapeutic range
0.2 - 1	2 - 10 (.1-.5 ml)[2]	mild tachycardia/ increase in cardiac output(CO); significant hypotension unlikely	therapeutic range in hypertensives with β blocking agent
1 - 2	10 - 20 (.5 - 1 ml)[2]	mild/moderate tachycardia; possible hypotension	maximum recommended dose range for hypertensives
2 - 10	20 - 100 (1 - 5 ml)[2]	moderate tachycardia/increased CO; mild/moderate hypotension; possible myocardial ischemia (MI)	above recommended safe pharmacologic dose levels
10 - 100	100 - 1000 (5-50 ml)[2]	moderate tachycardia/ increase in CO; moderate/severe hypotension; increased risk of MI	case reports of serious injury in adults
>100	>1000 (>50 ml)[2]	possibly fatal	one documented death

[1] based on a 10 kg child
[2] ml of two percent minoxidil liquid

The pharmacologic dose range used to lower blood pressure in hypertensive adults and children in combination with a &blocking to eliminate reflex tachycardia is 0.2 - 1 mg/kg. Significant hemodynamic effects are not expected at doses below 2 mg (0.2 mg/kg) in a 10 kg child. The dose range of minoxidil usually recommended for antihypertensive therapy (0.2 - 1 mg/kg) is expected to cause some vasodilation resulting in mild reflex tachycardia in a healthy normotensive child . Significant hypotension is unlikely unless reflex activation of the adrenergic nervous system and the renin-angiotensin system are not functioning optimally.

As the ingested dose of minoxidil increases above the usually recommended therapeutic range (>1 mg/kg), the undesirable effects on heart rate and cardiac output are expected to become more evident and prolonged. In addition, reflex adrenergic activation may no longer be able to counteract the primary minoxidil-induced vasodilation leading to an increasing risk of hypotension. Prolonged increases in cardiac output stress the oxygen demands of the heart while decreases in vascular resistance and blood pressure result in lower tissue perfusion and compromise the ability to deliver oxygen to cells. The outcome is lethargy and lightheadedness, with the possibility of myocardial ischemia and tissue damage,

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if left untreated. Because of the possilble adverse effects, the maximum recommended daily therapeutic dosage is 100 mg in adults and 50 mg for children under the age of 12 (an approximate dose range of 1 - 2 mg/kg). For an adult weighing an average 70 kg, the maximum recommended daily dose normalized to body weight is 1.4 mg/kg. The equivalent minoxidil dose for a 10 kg child is 14 mg.

Severe hypotension requiring emergency medical treatment and prolonged hospital stays have been reported in adults ingesting 10 - 20 mg/kg minoxidil. This would be about 100 - 200 mg for a 10 kg child and only 5 -10 ml (1 - 2 teaspoons) of a 2 percent minoxidil solution. Ingestion of the entire contents (60 ml) of the standard topical minoxidil package could be lethal to a young child.

Although uncommon, some conditions can increase susceptibility to the hemodynamic effects induced by minoxidil and increase the risk of serious injury at lower doses. Individuals with pre-existing cardiac, renal, or vascular abnormalities may be unable to adequately compensate for minoxidil-induced vasodilation and, thus, experience more severe hypotension. Pre-existing cardiac conditions may also increase risk of injury to the heart muscle as a result of prolonged tachycardia and increased cardiac output following minoxidil ingestion. Individuals already being treated with anti-hypertensive medications, particularly p-blocking agents, antiadrenergic drugs, or direct-acting vasodilators,, may undergo an exaggerated hypotensive response following ingestion of topical minoxidil.

It is recommended that preparations containing more than 14 mg of minoxidil be packaged in accordance with the special packaging provisions of the PPPA. Most healthy children under five years of age are believed to be reasonably protected from serious personal illness or injury following ingestion of minoxidil in quantities 14 mg or less. The 14 mg dose level corresponds to 1.4 mg/kg for a 10 kg child which is the the body weight normalized maximum recommended daily dose for the average 70 kg adult. Daily intake of quantities greater than this are not generally recommended as an anti-hypertensive agent in adults because of the increasing potential for adverse effects.

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