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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
HFA-305
Rockville, MD 20852

July 24, 2003

Re: Docket number 03N-0143
Syrup of Ipecac

Dear Sir:

I have followed the controversy over the use of gastric-emptying techniques in treating the poisoned patient for the last 40 years. What was once thought to be the standard of care, partly because it made good sense and had been done for nearly a century, the use of a tube to empty stomach contents and prevent absorption of substance, was replaced by the induction of emesis when "knowledge" that forced emesis with an emetic was as efficacious and safer. This standard of care then met with evidence that in many cases it was not efficacious and its use was replaced by a chemical absorbent. Recently doubt has been raised on the usefulness of this as well. This leaves the more senior toxicologist to wonder if we are beginning to go full circle or if it is simply best to leave the patient alone and to treat the complications if such occurs.

Although I agree that medicine must look at hard evidence of efficacy and potential side effects of all intended therapies, it may not always be possible to have complete data, particularly when dealing with circumstances with potentially dire outcome, or when adequate treatment for the complications, once they appear, is inadequate. All of the work done on this subject was done in the era before compliance issues with medications led to the introduction of sustained release products, and products with extremely narrow therapeutic windows, particularly when ingested in large quantities. In fact, all of the studies comparing absorbents with gastric emptying excluded from study such patients. This will continue to be a problem since I can not see how Institutional Review Boards would allow a study to be undertaken in which a potentially lethal ingestion of a substance will go without any attempt at gastric emptying despite no solid evidence of its

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efficacy, when the investigator admits that if the entire dose is retained there is not treatment that will insure 100% survival.

Efficacy studies of the use of syrup of ipecac give results that can be used either to show ineffectiveness or effectiveness depending on the reviewers ability to see the glass as half full or half empty. In fact, there really are very few published reports of research related to this issue, particularly few in which human victims are involved.

Arnold and his group[i] studied the effects of forced emesis or lavage on the recovery of salicylate administered into the stomachs of dogs. When ipecac was administered to dogs within 15 minutes of the administration of the salicylate, emesis occurred in under 30 minutes and the salicylate recovery averaged 45% with 50% experiencing recovery of 50% or more, 22% experienced the recovery of over 70%!
In another dog model studied by Abdallah and Tye[ii] when an optimal dose of ipecac was administered, as defined as producing emesis in 100% of the animals, 62% of the barium sulfate load was recovered if the emetic was administered at time zero, 44% and 31% at 30 and 60 minutes after the load of barium sulfate.

Looking at children as victims of accidental poisoning, Robertson[iii] showed that 100% of the children who were seen for treatment of poisoning and who received ipecac vomited, in 88% of the cases they vomited in under 30 minutes and 56% in under 15 minutes. There were no reports of toxicity in the over 1500 children who were in this sample. The study did reveal a problem with the technique, in the 150 cases in which a precise time of ingestion could be established, the ipecac was dispensed in the emergency department an average of over an hour after the ingestion. The consideration of the importance of this timing lead to the discussion of the format to distribute ipecac. The limitation in place at the time of Robertson's work included the fact that ipecac was then a prescriptive drug. In 1966 Shirkey[iv] in an editorial written after the Food and Drug Administration changed ipecac's status to over the counter, called for the widespread dissemination of ipecac into homes to avoid the delay in potential administration. He cautioned that strict attention be played to the dose used and avoidance of the fluid extract of ipecac, since he stated that almost all of the reported instance of toxicity resulted from the use of the latter preparation.

Further evidence of the efficacy of ipecac-induced emesis in children was presented by Corby in 1968[v] in which children who were thought to have ingested potentially toxic overdoses were given a tracer of 200 ml of magnesium hydroxide and then ipecac experienced emesis with a mean latency of 15 minutes post ipecac administration with the resultant recovery of a mean of 28% of the ingested dose. Unfortunately the authors did not state the length of time which expired between the toxic ingestion and the administration of the ipecac or how they ascertained that the entire dose of tracer was actually ingested.

As to the toxicities from ipecac, there are few reports in the literature of significant problems. I would be remiss to avoid this discussion, but have very little to base the discussion on. Smith and Smith[vi] reported a review of the literature and a case of a 4 year

old who expired after repeated doses of the fluid extract of ipecac in an attempt to induce emesis. A Medline search of the literature using the subheading of "adverse reaction" and either ipecac or charcoal as the main search term revealed 95 matches for activated charcoal and 65 for ipecac. In the ipecac citations retrieved there was one gastric rupture and death attributed to protracted emesis of over 24 hours in a child who had ingested 1-5 tablets of chlorpheniramine[vii], a marginal indication for ipecac, a young woman who developed pneumomediastinum and retropneumoperitoneum after persistent emesis following ipecac administration,[viii] and the report of protracted vomiting in 17.1% and diarrhea in 13% of 146 patients who had emesis induced at home and who were followed up by the poison center. In fairness there were 4 case reports of toxicities from abuse of ipecac.

When the adverse reactions of charcoal therapy are reviewed, there are 11 cases of severe gastrointestinal abnormalities including 6 requiring surgical intervention[ix,x,xi,xii,xiii,xiv,xv,xvi,xvii,xviii,xix,xx], 11 pulmonarycatastrophies including 2 deaths and one case of bronchiolitis obliterans,[xxi,xxii,xxiii,xxiv,xxv,xxvi,xxvii,xxviii,xxix]2 cases of severe hypernatremic dehydration associated with the combined use of charcoal and sorbitol, a frequently suggested combination,[xxx,xxxi] and a rather odd experience of corneal abrasions after activated charcoal[xxxii].

It is assumed that the earlier intervention to interrupt the absorption of drug the more effective the intervention. Several studies in the United States and abroad demonstrate significant delays in administration of activated charcoal to poisoning victims. These delays may be due to transit to the emergency department and institutional delays within the institution. These total delays often exceed one hour.[xxxiii,xxxiv,xxxv,xxxvi,xxxvii,xxxviii]. The use of gastrointestinal decontamination procedures in the home would be an obvious way to circumvent many of these delays. An effort at home administration of activated charcoal was undertaken in Boston, Mass by staff of the Children's Hospital and the Mass Poison System[xxxix]. Trained observers were dispatched to the homes of selected victims with activated charcoal and the parents were instructed to administer the activated charcoal to their children. Although the numbers of children were low, strikingly, none of the parents were able to convince their children to drink the dose recommended. An additional study of the feasibility of home administration of charcoal was undertaken by staff of the Fingerlakes Poison Center[xl]. Although compliance in this study was significantly better, there was still a 70% reported incidence of difficulty in administration of the charcoal with only 60% receiving the suggested dose. The reports of acceptance were made by the parent by telephone and was not directly observed. This was in contrast to previously reported studies concerning compliance with home ipecac such as that of Mowry in which compliance was greater than 92%, emesis commenced within 20 minutes and lasted for under an hour with 3 episodes of vomiting was the norm[xli]. Of interest is the renewed interest in this subject and the report by Scharman involving **simulated** poisoning situations in which parents demonstrated limited ability to insure administering a dose of charcoal mixed in a carbonated beverage.[xlii] Seventy three percent of the mothers were unable to get their children to drink more than 50% of the calculated appropriate dose and sixty percent drank less than 25% of the dose. If this work was done in an ideal setting without the stress and anxiety of a parent worried her

child would become very sick or die, I can only imagine the difficulty in adminsitering a dose of activated charcoal live, in a really tense situation!

Recently Spiller and Rodgers reported greater success but as in the Fingerlakes study, there was no corroboration of compliance by an independent observer, the researchers depended upon family telephone report of success.[xliii]

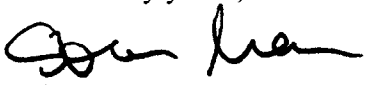
As I stated earlier in this correspondence, I am concerned about the potential for losing a trusted friend in the treatment of poisoned patients. Although the use of ipecac has dwindled, I do believe that there is still a real place for it. None of the studies of the efficacy of activated charcoal involve today's sustained release and metered release preparations. Since most of the newer drug delivery systems were designed to prevent the interference with absorption by food and other substances, it is unclear whether a single or multiple doses of activated charcoal will prove sufficient to prevent the absorption of drug over 24 or more hours. I do not need reams of scientific evidence to convince me that if I can recover intact drug delivery systems, then drug is not available for absorption.

Why then not simply make syrup of ipecac into a prescriptive drug? First, that would return the status to the way it was originally, until it became obvious that a potentially useful approach to dealing with a poisoned patient was being missed because of difficulty obtaining the substance. Further, educational efforts at having it widely available while it was a prescription substance were unsuccessful. Once it became an over the counter product, compliance with keeping the substance in the home increased dramatically. Some may state that the substance became too available and that this produced the epidemic of anorexia nervosa and bulimia. In an era of evidence-based medicine I would like to see this data. We know of some limited reports of its use in this population, but over what size population is it being used? What evidence do we have that making ipecac a prescriptive drug will prevent this abuse? Our efforts at restricting other abused drugs and substances have not been terribly successful at anything except producing a new class of criminals.

What if the FDA decides to make ipecac a prescriptive substance but no company will risk the funds to get it relicensed? If this happens, it will be gone forever.

I urge the panel to consider carefully the consequences of this action.

Sincerely yours,



Steven Marcus, MD

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