Acute toxicity studies of Lomotil and Neomycin showed LD_{50} in the adult mouse administered intragestrically to be greater than 1 gram/kg for either drug alone or as a mixture. Intraperitoneally, LD_{50} in the mouse was greater than 1 gram/kg for Lomotil, 240±24 mg/kg for neomycin and 315±32 mg/kg for the mixture (1 part of Lomotil to 50 parts Neomycin). In the rate a double peak of 50% mortality made precise LD_{50} calculation of Lomotil alone impossible. These peaks came at 130 mg/kg and 450 mg/kg both orally and I.P. LD_{50} for neomycin and in the mixture were greater than 1 gram/kg orally but 420±64 mg/kg for neomycin and 465±47 mg/kg for the mixture when given I.P. There appears to be no potentiation of LD_{50} between the two drugs.

Evaluation

Both reproduction studies indicate that there is no teratogenic effect of Lomotil when fed during pregnancy but that very high doses adversely affect the fertility of the adults (no studies on fertility of offspring) when fed for long periods (60 days prior to mating).

However, there is no evidence from the report of the laboratory as to the form in which the drug was given. If the studies were performed on the mixture (2.5 mg diphenoxylate to 0.025 mg atropine sulfate) then the results suggest a statisfactory margin for safe usage in pregnancy. If they were performed only on the diphenoxylate they should be repeated using the mixture. There is also no indication as to whether the syrup or dry material was used. There might possibly be an increased absorption of either or both drugs from the syrup. (The deaths in children, except those due to accidental ingestion of huge doses, followed administration of the syrup rather than the tablet form).

Acute and subacute studies of toxicity in the newborn should be run concurrently with adult studies to determine relative toxicity of the mixture in both forms—dry mixture and syrup. Until the comparative newborn vs. adult studies are reported and evaluated, it is urgently suggested that a stronger contraindication be placed in the labeling against administration to infants and young children.

L. L. PHILLIPS, Ph. D.

SUMMARY OF REPORT

Date Summary Completed: 9/11/67.
NDA 12-462 & 12-699. G. D. Searle, Chicago, Ill.
Original Approval Date: 12-462 9/19/60; 12-699 1/17/61.
Name of Drug.—Trade—Lomotil.
Generic—Diphenoxylate-HCl with atropine sulfate.
Dosage Forms and Route of Administration.—To 20 mg/day for adults, orally; children from 3 mg (3-6 months old); to 10 mg/day (10-12 years old).
Category or Use of Drug.—Antiperistaltic.

Material Reviewed

Report entitled "Acute oral toxicity study in weanling rats, of diphenoxylate MCl, Lomotil Powder, and Lomotil Liquid.

The report shows that diphenoxylate HCl alone has an LD50 of less than 117 mg/kg while the Lomotil Powder has LD50 of 47 (males) to 71 (females) mg/kg in 25 day old weanling rats. This is from 2 to 10 times the toxicity found in the adult LD50 (130-450 mg/kg).

The Lomotil Liquid has an LD50 equivalent to 22.8 ml/kg or 11.4 mg/kg in the weanling rats. This is 4 to 6 times the toxicity evinced by the dry powder.

Most of the deaths of rats with the powder occur within 2-5 days following administration of the drug and the dose response curve is flat. This tends to indicate that there may be occasional extreme susceptibility to the drug or increased absorption.

On the other hand after Lomotil Liquid the animals usually died within 24 hours of dosage and the dose-response curve was steeper. Both of these facts indicates absorption of the drugs to be more rapid and more uniform from the liquid than from the powder.

Clinical Evaluation

These studies make it evident that Lomotil is more toxic to the young animal than to the adult and that the Liquid form is more toxic than the powder—perhaps due to increased absorption from the gastro-intestinal tract. This increased