

Laboratory data reveal significant blood levels achieved rapidly and persisting over a six-hour period with rectally administered, low volume concentrated solutions of aminophylline (Somophyllin®).

RECTAL AMINOPHYLLINE (BLOOD LEVELS WITH CONCENTRATED SOLUTIONS)

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AMINOPHYLLINE (theophylline with ethylenediamine) is one of the most useful drugs employed in the management of bronchial asthma. Its therapeutic effects are closely related to its blood level.¹ This should approximate from 5 to 9 mcg/ml in serum. Segal et al in 1949 demonstrated that a rectal solution of 0.5 gm of aminophylline in 15 cc water yielded a significant degree of protection against histamine and methacholine induced bronchospasm in asthmatics, equal or superior to that produced by the intravenous injection. This protection occurred with theophylline blood levels of 500 μ g/100 ml or more.³

The present study was conducted to assess the blood levels obtained with a concentrated solution of aqueous aminophylline (60 mg per cc) —

Somophyllin® administered rectally. A small volume of 5.0 cc contains an average dose of 300 mg, and is easily administered with a disposable small plastic syringe and rectal tip.

Methods and Materials

Eleven patients with chronic stable bronchial asthma of variable degrees of severity were selected for study. Clinical stability was confirmed by clinical and spirometric data. In all patients, xanthine drugs, barbituates, salicylates, and xanthine beverages were discontinued 24 hours prior to the study.

At zero time, a control plasma was drawn. Immediately thereafter, 5 cc of concentrated theophylline monoethanolamine (300 mg/5 cc), Somophyllin® was administered rectally over a one-minute period followed by a five-minute period of rest. Thereafter, vital signs and clinical observations for side effects were recorded at intervals coincident to withdrawal of serial blood samples at 15, 30, 60, 120, and 360 minutes. The serum concentration of theophylline was assayed by the ultraviolet spectrophotometric method of Schack and Waxler employing a Beckman DU spectrometer.¹

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TABLE I. SERUM THEOPHYLLINE CONCENTRATIONS VERSUS TIME*

Time (minutes)	Serum Theophylline ($\mu\text{g}\% \pm 1 \text{ SD}$)
0 (K)	2.3 ± 1.3
15	266.4 ± 164.9
30	472.8 ± 89.1
60	560.5 ± 110.6
120	556.6 ± 143.6
240	502.6 ± 205.2
360	360.6 ± 165.7

*Single dose of 300 mg (5 cc solution) rectally of Somophyllin®.

Results
Patient Population

Of the eleven patients studied, the mean age was 56 years with a range of 31 to 69 years. The mean weight was 68.0 kg.

Serum Theophylline Concentrations (Table I)

Following a single rectal dose (300

mg/5 cc) of the concentrated theophylline (Somophyllin®), the serum concentrations rose rapidly in 15 minutes, reaching a mean value of $266.4 \pm 164.9 \mu\text{g}\%$. Serum levels of $560.5 \pm 110.6 \mu\text{g}\%$ at 60 min appeared peak, statistically greater than in 15 ($P < 0.02$) and 30 min ($P < 0.05$). No statistical differences were observed between 60, 120, or 240 minutes. At three hours, a modest decline was recorded with a mean serum level of $360.6 \pm 165.7 \mu\text{g}\%$.

Kw, which reflects the initial absorption of the drug, and which is defined as the serum theophylline concentration (in $\mu\text{g}\%$) per minute (measured over time 0 to 30 min) per mg of administered dose was 5.2×10^{-2} . Comparative data abstracted from the literature (Table II) indicate that over a comparable time period for equivalent administered doses, concentrated rectal solutions are equivalent to other preparations in rising to effective blood levels.⁴⁻⁷ However, comparative studies

TABLE II. COMPARISON OF THEOPHYLLINE ABSORPTION RATES

Reference		Kw ($\mu\text{g}\%$ serum theophylline min/mg) $\times 10^{-2}$	Actual Peak Level* (time)	Preparation	Total Administered Dose (mg)
This paper	adults	5.2	560.6 (1 hr)	Rectal Solution	300
	adults	3.4	672 (2 hrs)	Rectal Solution	450
		5.2	900 (15 min)	IV	450
5	children	1.5	369 (4 hrs)	Suppository	500
		10.0	1171 (1 hr)	Rectal Solution	288 (> 11 mg/kilo)
		8.9	932 (1 hr)	Rectal Solution	285 (8-10 mg/kilo)
		6.8	660 (1 hr)	Rectal Solution	286 (< 8 mg/kilo)
6	adults	10.3	1231 (1 hr)	PO (Elixophylline)	400
7	adults	3.7	840 (3 hrs)	PO (Cardalin®)	300
		5.6	1285 (3 hrs)	PO (Cardalin®)	600
8	adults	8.0	600 (30 min)	IV	250 mg
		2.1	660 (2 hrs)	IM	500
		3.7	325 (1 hr)	IM	250
		0.26	390 (4 hrs)	Suppository	500
		2.6	260 (1 hr)	Oral, uncoated tablets	200

(* μg per 100 cc serum)

PO = by mouth

IV = intravenous

IM = intramuscular

within the group with these other preparations were not directly performed.

Discussion

It is generally accepted that rectal dosing is an effective way to administer aminophylline for the relief and prevention of moderate attacks of bronchial asthma.^{8,9} Suppositories of aminophylline are frequently unreliable because of variable absorption rates and toxicity particularly in infants and children. Effective theophylline blood levels were seldom reached after 0.5 gm suppository.¹⁰ Solutions of aminophylline are rapidly absorbed from rectal vascular plexus blood stream, reaching the pulmonary circulation. The aminophylline does not enter the upper gastrointestinal tract and short circuits the liver; hence, avoids some of the unpleasant side reactions observed after oral aminophylline—namely nausea, vomiting, and/or abdominal distress. Furthermore, the dosages can be accurately controlled and easily changed from time to time by dilution with water. This is particularly of value in management of children and others subject to aminophylline side effects.

Barach reported effective results in 200 patients with bronchial asthma using a rectal instillation of dilute aminophylline solution (300 mg per 15 cc)⁸. Subsequently, other investigators reported effective clinical results with disposable rectal units employing similar dosages but in 25 to 50 cc amounts.¹¹⁻¹³ In an attempt to minimize the technical, and aesthetic aspects of rectal administration, a concentrated form of aminophylline, Rectalad® (100 mg/cc) in disposable units was evaluated by Traverse and Segal. Effective and long-lasting blood levels of theophylline were observed in these studies.¹⁴

The rapidity of onset, peak of blood

level, and persistence of blood levels after Somophyllin® clearly indicate that effective therapeutic blood levels are achieved with the rectal administration of this concentrated form of aqueous aminophylline in small volume. The rapidly achieved blood levels with persistence of effective therapeutic levels over a six-hour period provide a relatively simple and inexpensive therapeutic modality for administering aminophylline.

Summary

The striking clinical effectiveness of rectally administered, low volume concentrated solutions of aminophylline, (Somophyllin®) has been observed by one of us (MSS) over a period of six years in the management of patients with chronic bronchial asthma. These observations prompted a study to determine its rate of absorption on peak levels, and persistence of effective theophylline blood levels. The laboratory data revealed significant theophylline blood levels, achieved rapidly and persisting over a six hour level; thus explaining the effectiveness of this therapeutic aid for patients with bronchospasm. The dosages must be carefully determined for each patient in order to avoid any aminophylline toxicity.

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