Theophylline-Induced Hypercalcemia

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Sixty patients with theophylline toxicity were hospitalized during a 2-year period. Eleven patients had hypercalcemia; their calcium levels returned to normal as theophylline levels fell to therapeutic or subtherapeutic levels. Serum calcium levels also fell significantly in three additional patients with theophylline toxicity, although the initial serum calcium concentration was not outside normal limits. A significant increase in serum calcium levels associated with therapeutic levels of theophylline in normal volunteers was reversed by propranolol. It appears that theophylline causes elevation of serum calcium by a system subject to beta-adrenergic regulation.

THEOPHYLLINE, a cyclic nucleotide phosphodiesterase inhibitor (1), permits accumulation of tissue cyclic adenosine monophosphate (cyclic AMP), an effect commonly thought to contribute to its effectiveness in the treatment of bronchial asthma. It is also believed that the calcemic and phosphaturic effects of parathyroid hormone are mediated by cyclic AMP. When patients hospitalized for theophylline toxicity had hypercalcemia that declined to normal after theophylline was discontinued, with the fall in calcium paralleling the fall in theophylline concentration, we wondered whether the apparent hypercalcemic effect of theophylline might be related to its effect on cyclic AMP either by increasing secretion or enhancing the target organ effects of parathyroid hormone. Our results suggest that the hypercalcemia of theophylline intoxication may be mediated via adrenergic mechanisms and is compatible with enhancement of parathyroid hormone actions.

Materials and Methods

Patients admitted to Norfolk General Hospital and DePaul Hospital for theophylline toxicity (serum theophylline levels, > 20 μg/mL) over a 2-year period were included in the study. Any patient also using sympathomimetic agents or corticosteroids, or with previously documented hypercalcemia, was excluded from the study. Adequate hydration was assured before studies were begun by the history and physical examination or by administration of intravenous fluids. All patients used slow-release preparations of anhydrous theophylline (Slophylline; William H. Rorer, Inc., Fort Washington, Pennsylvania; or Theodur; Key Pharmaceuticals, Inc., Miami, Florida) for chronic obstructive pulmonary disease. None of the patients had evidence of tuberculosis, sarcoidosis, or other granulomatous disease of the lungs.

Normal volunteers participated in two experimental protocols identical except for the dosage of theophylline (Slobid; William H. Rorer, Inc., Fort Washington, Pennsylvania). The protocols consisted of a control period followed by theophylline administration, either 200 or 400 mg twice a day, for 7 days; during the last 2 days of the protocol, propranolol, 40 mg every 6 hours, was also given. Diet could not be closely controlled but beverages containing caffeine, if consumed, were kept constant throughout the period of observation. Serum or 24-hour urine specimens for theophylline, calcium, phosphorous, creatinine, and cyclic AMP levels were collected during the control period, at the end of the theophylline-alone period, and on the last day of theophylline-propranolol administration. Samples were assayed immediately or kept at -20 °C until assays could be done.

Serum and urine calcium levels were determined by atomic absorption spectroscopy (2). Ultrafiltrable calcium was analyzed by atomic absorption spectroscopy after preparation of samples using the Amicon MPS1 ultrafiltration system (Amicon Corporation, Danvers, Massachusetts (3). Urine and plasma cyclic AMP levels were determined by radioimmunoassay using commercially available kits (Diagnostic Products Corporation, Los Angeles, California), and nephrogenous cyclic AMP was calculated by the method of Broadus and associates (4). Serum parathyroid hormone was determined by radioimmunoassay using the Nichols Institute Diagnostic C-terminal parathyroid hormone kit, and theophylline was measured by enzyme-linked immunosorbant assay, also by kit (Syva Co., Palo Alto, California).

Results

Eleven of sixty patients hospitalized for theophylline toxicity had hypercalcemia. Calcium concentration fell to normal within 2 days after stopping theophylline administration as serum theophylline levels reached therapeutic or subtherapeutic levels. Serum calcium concentration in three additional patients hospitalized with theophylline toxicity were within the normal range initially but a significant decline was seen after theophylline was discontinued. Parathyroid hormone levels were within normal limits during the hypercalcemic period and did not change significantly after calcium levels returned to baseline ($p > 0.05$). Ultrafiltrable calcium initially was increased also in the few patients in whom it was measured and the concentration showed a significant correlation ($p < 0.02$). A more significant correlation ($p < 0.001$) was noted when log concentration of serum theophylline was plotted versus serum calcium (Figure 1), suggesting a log-dose-response characteristic of biologic systems.

In the studies involving normal volunteers, administration of theophylline was associated with a small but clearly significant rise in calcium (9.2 to 9.9 mg/dL; $p < 0.05$) after the 400 mg twice-a-day dosage schedule for 5 days. The addition of propanolol abolished the calcemic effect of theophylline. Theophylline levels of 10 μg/dL or greater were obtained on the 400 mg twice-a-day schedule. Only one of the five normal volunteers reached therapeutic theophylline levels on the manufac-

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Table 1. Effect of Theophylline at Two Dosage Levels on Serum Calcium Levels in Five Normal Men*

	Serum Calcium Level	Ultrafiltrable Calcium	Nephrogenous Cyclic Adenosine Monophosphate	Parathyroid Hormone
Study 1	*mg/mL*	*mg/dL*	*ng/24 h*	*pg/mL*
Control	9.3 ± 0.3	...	1.1 ± 0.6	327 ± 95
Theophylline	9.1 ± 0.3	...	1.2 ± 0.5	316 ± 86
Theophylline and propranolol	9.3 ± 0.6	...	1.4 ± 0.7	348 ± 57
Study 2				
Control	9.3 ± 0.3	4.8 ± 0.3	0.9 ± 0.4	235 ± 76
Theophylline	9.9 ± 0.2†	5.4 ± 0.3‡	0.8 ± 0.5	230 ± 58
Theophylline and propranolol	9.2 ± 0.1	5.0 ± 0.1	1.3 ± 0.2	201 ± 67

* The two studies were identical except that theophylline dosage was 200 mg twice a day in Study 1 and 400 mg twice a day in Study 2. The mean serum theophylline level was 8.0 ± 4 μg/mL during Study 1 and 13.8 ± 3 μg/mL during Study 2. All values are mean ± SE.
† $p = 0.01$.
‡ $p = 0.05$.

turers' recommended lower starting dose of 200 mg twice a day (Slobid), and there were no consistent changes in serum calcium on the lower dosage ($p > 0.05$). Significant changes in parathyroid hormone levels, urinary phosphorus, urinary calcium, or nephrogenous cyclic AMP were not seen during treatment with theophylline at both dosage levels with or without the addition of propanolol (Table 1).

Discussion

Several studies indicate that calcium metabolism is altered by theophylline both in animal models (5-7) and in-vitro systems (8, 9), but the mechanisms involved have not always been well delineated or understood. Our study shows a correlation between theophylline intoxication and calcium levels that follow a log dose-response type of relationship suggesting more than casual association. Theophylline failed to increase serum calcium levels detectably unless theophylline levels reached at least those concentrations associated with relief of bronchial asthma.

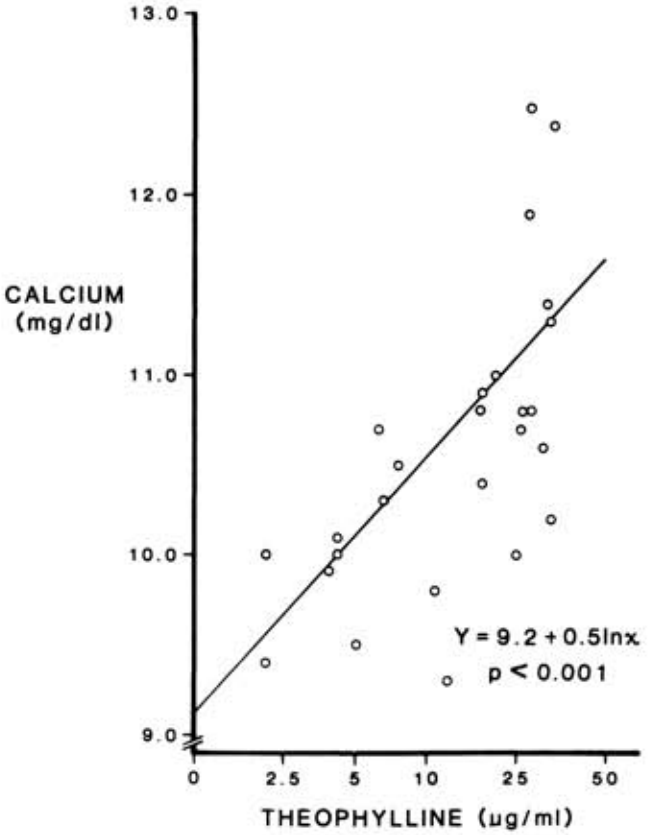

Figure 1. Relationship of serum calcium level to log serum theophylline level of patients hospitalized for theophylline toxicity before and after cessation of treatment ($r = 0.569$).

The fall in serum calcium levels after concurrent administration of propanolol suggests that an adrenergic mechanism is involved in the calcemic effect of theophylline and supports the concept that at least a part of the calcemic effect of parathyroid hormone may be via adrenergic receptors. As there was no significant change in parathyroid hormone concentration, it seems likely that theophylline hypercalcemia occurs due to enhancement of the effects of available parathyroid hormone. It is curious that there was no compensatory fall in parathyroid hormone concentration when serum calcium increased, but we may have been unable to observe the changes in parathyroid hormone due to the long half-life of the C-terminal fragment. Finally, the calcemic effects of theophylline may be through mechanisms independent of parathyroid hormone and may become important only in a person with toxic levels of theophylline. Further, it is not clear why some persons remain normocalcemic with theophylline levels that are associated with hypercalcemia in others.

Colin and associates (10) saw increases in urinary nephrogenous cyclic AMP, urinary phosphate, and calcium after a bolus injection of theophylline. These effects were not seen in our patients or volunteers on chronic or subacute administration of theophylline, and the difference may be due to routes of administration or the period of time over which theophylline was administered. Nevertheless, their observations support the concept of tissue stimulation or release of cyclic AMP by theophylline. At the osseous level, this effect could conceivably result in hypercalcemia when exposed to prolonged presence of supratherapeutic concentrations of theophylline.

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