

Drug Interactions I:

Folic Acid and Calcium Gluconate

Keyphrases □ Drug interactions—folic acid and calcium gluconate, low concentrations □ Folic acid—interaction with calcium gluconate, low concentrations □ Calcium gluconate—interaction with folic acid, low concentrations

To the Editor:

The interaction of folic acid and calcium salts is well documented (1–5). These references state that these compounds combine to yield a precipitate, but quantitative information on this interaction is lacking. Thus, it is of interest to determine the extent of this interaction at high dilutions and to investigate its reversibility with ethylenediaminetetraacetic acid (I), a known calcium-sensitive ligand. This study is important in view of the possible use of these agents in intravenous admixtures in pediatric patients in which a precipitate may not be obtained. This communication reports the results of a preliminary study that showed that calcium gluconate does inhibit significantly the reactivity of folic acid at low concentrations when a precipitate is not apparent.

The official assay (6) was modified by replacing the 2-min centrifuge period with a 10-min shaking period on a mechanical shaker¹. The procedure yielded 4 μg of folic acid (mean = 0.1 μg , $n = 16$). The interaction procedure was conducted by diluting a volume of the same intravenous solution of folic acid² with 3.03% K_2HPO_4 to yield a solution containing 10 μg of folic acid/ml. This solution was treated with a volume of calcium gluconate solution³, suitably diluted to yield the appropriate concentration of calcium ion (0.5, 1, or 10 $\mu\text{g}/\text{ml}$). This mixture was used as the assay preparation in the official assay after the volume was adjusted to 5 ml with distilled water. The quenching procedure was conducted as follows. After exactly 10 min, a quantity of I equimolar to the calcium concentration was added to the folic acid–calcium assay preparation, the volume was adjusted to 5 ml with distilled water, the preparation was mixed thoroughly, and the assay was followed as indicated previously.

Compound I in the same concentrations did not interfere with the folic acid determination when calcium gluconate was omitted (Fig. 1). As noted, the quantity of folic acid recovered by pretreatment with calcium gluconate diminished linearly ($T = 26^\circ$, $K = 0.228 \text{ min}^{-1}$). Furthermore, this folic acid–calcium interaction can be reversed quantitatively by the addition of I.

This study demonstrates that the folic acid–calcium

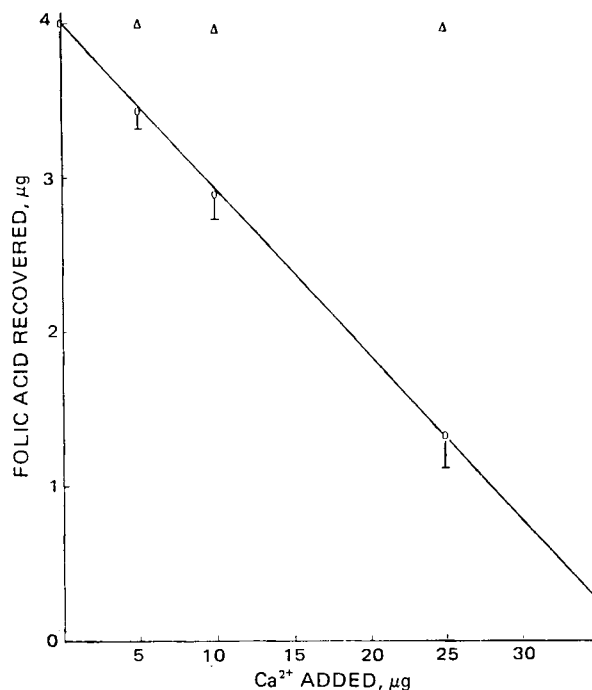


Figure 1—Effect of calcium gluconate on the folic acid concentration (10 $\mu\text{g}/\text{ml}$). Folic acid concentrations (○) (mean + or – SD, $n = 16$) are shown as a function of the micrograms of Ca^{2+} added. Pretreatment with ethylenediaminetetraacetic acid (Δ) also is shown.

interaction is significant at all concentrations, regardless of whether the interaction yields a precipitate. The stability constant of the folic acid–calcium interaction and the effect of pH on the reaction are being investigated further.

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¹ Model 6000, Eberbach.

² Folvite, Lederle.

³ Calcium gluconate injection (10%), Parke-Davis.