Simplified Simultaneous Determination of Valproic Acid and Ethosuximide in Serum by Gas-Liquid Chromatography

To the Editor:

Valproic acid (VPA) and ethosuximide (ES) are currently monitored in the serum of epileptic patients being so treated (1, 2). Two gas-chromatographic methods have been proposed for simultaneously measuring these two drugs (3, 4); in them, the organic extract must be concentrated by evaporation before chromatography. This incurs some loss of these relatively volatile compounds, a disadvantage that can be overcome if isoamyl acetate is added to the organic extract (3).

Van der Kleijn et al. (5) proposed that the ES be extracted into a small volume of solvent, such that no concentration would be required. Sufficient extraction efficiency is achieved by adding saturated KH2PO4 solution to the sample.

We have found that this suggestion could easily be applied to other drugs, such as VPA, paramethadione, trimethadione, dimethadione, and ethylphenacemide. Here we report the gas-liquid chromatographic determination of VPA and ES after NaH2PO4 is added to the sample and it is extracted into a small volume of chloroform.

Prepare the following internal-standards solutions: 200 μL of 2-methyl-2-ethylcaproic acid (not commercially available; kindly supplied by Dr. J. Meijer, Heemstede, The Netherlands) and 150 μg of α,α-dimethyl-β-methylsuccinimide (Aldrich Chem. Co., Beeese, Belgium 2340; cat. no. 16350-3) per liter of reagent-grade chloroform. This solution, stored refrigerated, is stable for at least a month.

Mix 200 μL of serum and 200 μL of a saturated NaH2PO4 solution in a conical glass centrifuge tube. Add 75 μL of the internal-standards solution. Shake the tube on a vortex-type mixer for 30 s and centrifuge for 5 min at 4000 X g. Inject 1.5 μL of the organic extract into the chromatograph. For the determination of “oxypurines” (hypoxanthine plus xanthine) in urine and blood plasma (Analyst 93, 354–362 (1968).

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Dimenhydrinate Interferes with Radioimmunoassay of Theophylline

To the Editor:

I wish to report the positive interference of dimenhydrinate with a theophylline radioimmunoassay (RIA). A 44-year-old woman, admitted to the hospital with steroid-dependent asthma, had been treated as an outpatient with prednisone, theophylline, and dimenhydrinate (Dramamine, Searle). She was treated with, and responded to, intravenous theophylline and methylprednisolone sodium succinate.

Theophylline in serum was assayed by an RIA kit procedure (Clinical Assays, unmodified), by enzyme-multiplied immunoassay (EMIT, Syva), and by liquid chromatography, with the following results:

<table>
<thead>
<tr>
<th>Day</th>
<th>Apparent theophylline, mg/L RIA</th>
<th>EMIT</th>
<th>LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>59.7</td>
<td>21.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Day 2</td>
<td>57.2</td>
<td>25.6</td>
<td>24.2</td>
</tr>
</tbody>
</table>

Though the patient had apparent toxic concentrations of theophylline by RIA, there was no clinical evidence of...