about the sensitivity and specificity of the test. Hence the following remark in our preamble: "The test is a good one, as far as such a test can be, but it is imperfect, because false-negative and false-positive results both occur. In other words, it is not an infallible test." In several places the statement indicates that "MSAFP is a screening test and is not diagnostic".

As Shier mentions, what we require is a direct biochemical test for Down's syndrome, one with high sensitivity and high specificity. That is why many of us are investigating other, more specific ways of identifying pregnant women with an increased risk for having a child with Down's syndrome. However, until such a method is available we consider MSAFP screening to be satisfactory, provided that patients are adequately informed about its advantages and disadvantages and that their counseling is nondirective and supports their moral and ethical beliefs.

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Binding of bismuth to cell components: clue to mode of action and side effects

W e have noted several reports that bismuth salts are being widely prescribed as curative or prophylactic agents for patients with gastroenteritis and gastric ulcer, although the toxicity of some bismuth preparations is still a problem.

We have used Bi\(^+3\) as a stain of fixed tissue for light and electron microscopy and are now using it in vivo to characterize certain cell components. Despite the insolubility of most bismuth salts, Bi\(^+3\) reacts with living cells even at dilutions as low as 100 mg/L to give enough contrast for some components to become visible in thin sections viewed by electron microscopy. The following is a partial list of these components: interchromatin granules, nucleoli, mitochondrial granules, centrioles, membrane specializations such as synapses and microvillar tips, contracting membranes such as midbodies and spreading acrosomes, Golgi complex beads (not in all cells) and ferritin.

Both in the tissue staining of
fixed material and in the in-vivo binding to fractions of whole cells the reactions are characteristic for particular cell components. These components are therefore the ones that would most certainly be affected by the therapeutic administration of bismuth, which may be presented at even higher concentrations than those in the staining solutions we use (a commonly available preparation contains 17.5 g/L).

It seems likely that therapeutically administered bismuth would give rise to subcellular distributions similar to those that we have observed experimentally since bismuth particles are known to be endocytosed by gut cells,6 and serum levels may exceed 0.1 mg/L.7 The concentration of bismuth by these cell components may give a clue to the mode of action of this element and the reason for side effects. For example, the binding of Bi3+ to synapses would be expected to lead to neurotoxic effects,8 which are seen even with blood bismuth levels of less than 0.1 mg/L,9 and the formation of renal nuclear inclusions10 might be expected from the reaction of bismuth with nuclear components and the high levels excreted in urine.10

The specific binding by several important cell structures should sound a note of caution in the widespread therapeutic use of bismuth. These are not the localizations expected for a silver bullet of healing.

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References


Systemic absorption of intraurethral lidocaine

We noted with interest Dr. M.B.M. Sundaram's report describing an 80-year-old man who on two occasions experienced a seizure within minutes after the intraurethral instillation of lidocaine (Can Med Assoc J 1987; 137: 219–220). Although blood lidocaine concentrations were not determined, we agree that the seizures were most likely a toxic effect of the drug.

Recently we quantitated lidocaine in the blood of a 68-year-old man after intraurethral instillation of 10 ml of 2% lidocaine jelly to facilitate passage of a catheter to obtain a urine specimen for toxicology screening. The blood specimen was obtained 1 to 2 hours later. Qualitative urine analysis yielded a strongly positive result for lidocaine, and gas chromatographic analysis of the serum demonstrated a lidocaine concentration of 0.2 μg/ml, well below the therapeutic range of 1.5 to 5.5 μg/ml and thus unlikely to produce toxic effects. Subjective toxic effects on the central nervous system occur at levels of 3.0 to 5.0 μg/ml and objective adverse manifestations at 6.0 to 10.0 μg/ml.1

However, our patient's peak serum lidocaine concentration was probably higher than 0.2 μg/ml. Serum concentrations of lidocaine peak 66 minutes after oral administration,2 but lidocaine's clinical pharmacokinetics after intraurethral administration are unknown. We speculate that absorption across the urethral mucosa would be rapid because of the rich vascular supply and that peak systemic concentrations would be higher by this route owing to absence of a hepatic first-pass effect. For example, lidocaine concentrations peak 13 minutes after endotracheal administration.3

The presence of lidocaine in the blood after its intraurethral administration has been qualitatively shown in the past.4 Since this agent is commonly used to facilitate catheterization of the urinary bladder, its pharmacokinetics in this situation should be characterized so that toxic effects can be prevented.

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References