Drug Repackaging

I would like to comment on the editorial[1] "Bureaucratic Overkill," which appeared in the May issue of this Journal. I feel strongly that some agency must regulate drug repackaging in hospital pharmacies.

I am actively engaged with a local hospital in determining the stability of drugs after repackaging in unit dose forms. We have found that serious stability problems are possible unless proper quality control procedures are followed. For example, a number of tablets had rusty spots because the repackaging machine was not cleaned properly. Furthermore, repacked neomycin sulfate tablets had absorbed about 4.5% of moisture in less than 1 month and had become discolored. Tablets in the original container (same lot) did not change color and absorbed very little moisture. The expiration date was still a couple of years away. Moreover, aminophylline tablets had problems similar to neomycin sulfate tablets. Needless to say, all of these dosage forms had to be removed from the shelves.

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Thiazide Bioavailability Studies

There is a paucity of reports on the absorption and mode of elimination of the thiazide diuretics. However, there is general agreement[1,2] that when a thiazide is dissolved in water (in which it is slightly soluble), hydrolysis occurs and an equilibrium is established. The extent of this hydrolysis *in vivo* varies with the thiazide. Our studies reveal that for cyclothiazide and methyclothiazide, it varies from one individual to another and even in the same individual at different times.

The hydrolysis product common to the thiazides is 4-amino-6-chloro-*m*-benzenedisulfonamide (I). This compound, which is more soluble in water than the thiazides, is absorbed and displays diuretic activity[3]. According to Tust[4], "in saline-loaded rats the diuretic activity is equivalent to chlorothiazide." We found that I is excreted slowly in humans and can be measured in urine 96 hr after a 250-mg dose of chlorothiazide.

The more potent thiazides normally hydrolyze more extensively *in vivo* to furnish I in the urine. Examination of the urine of 28 male subjects who had been dosed with cyclothiazide, using the Bratton–Marshall colorimetric method, revealed that the 24-hr urinary excretions of I plus cyclothiazide, calculated as thiazide, ranged from 10.3 to 57.8% (average 25.4) of the ingested dose. Most of the urines were also assayed by a high-performance liquid chromatographic (HPLC) method to measure cyclothiazide and I. The urines examined contained 5–35% of the cyclothiazide as I.

When urines are extracted with ethyl acetate to recover thiazide, I, even as its hydrochloride salt from urines acidified with hydrochloric acid, is also essentially quantitatively recovered. The Bratton–Marshall method measures the I formed by hydrolysis of the thiazide both *in vivo* and *in vitro* and, therefore, usually furnishes higher urinary levels than the HPLC method when only thiazide is assayed.

Interferences by urinary constituents when the Bratton–Marshall method was used for the determination of sulfonamides in the urine were recognized early by Marshall *et al.*[5]. As more potent thiazide diuretics than chlorothiazide were subsequently introduced, less dilution of the urine was possible and these interferences became more troublesome[6]. The purple color, which develops more slowly (and is more stable) than the red color from the Bratton–Marshall, is produced by certain urinary constituents[1]. The purple color from human urine displays a broad absorption band with a maximum at 545 nm. However, by a special extraction procedure and measurement of the red color at 500 nm, the interference from urinary constituents in humans can be substantially eliminated.

Urine samples are made alkaline with sodium hydroxide solution and heated on a steam bath for about 3 hr to destroy emulsifying components, which frequently produce very stable emulsions with urine and ethyl acetate. The urine samples are then made acidic with an excess of hydrochloric acid, which increases the salt concentration and favors more complete extraction of the thiazide and I hydrochloride by ethyl acetate. The ethyl acetate is separated, washed with a small volume of distilled water, and then extracted quickly (10–15 sec) with two portions of 0.1 *N* NaOH.

The sodium hydroxide extracts are combined and allowed to stand for about 30 min, which permits hydrolysis of dissolved ethyl acetate and a drop in pH to about 8.0. This slightly alkaline solution is then extracted with fresh ethyl acetate. The ethyl acetate layer is separated and evaporated to dryness with a stream of air or nitrogen. The residue is completely hydrolyzed to I by treatment with 5 *N* NaOH and evaporation to dryness on a steam bath. The residue from this treatment is dissolved in strong hydrochloric acid[1] to a predetermined volume, and the I is diazotized in the usual manner and coupled with *N*-1-naphthylethylenediamine. The absorbance at 500 nm is determined 15–30 min after the diamine solution has been added.

This reaction is more complex than a simple diazotization[2]. Examination of the red color produced by TLC on silica gel revealed the presence of at least four components. The absorption maximum of the red color is 510 nm; by measuring absorbance at 500 nm instead of at 518 nm, as is frequently used, less than a 4% loss in intensity is encountered. However, measurement at 500 nm decreases any small interference from human urinary constituents by about 40%.

Although the HPLC method will measure a thiazide in the urine with good precision[7], I believe a more meaningful measure of bioavailability of the thiazide diuretics, especially those given in smaller doses where more of the drug is hydrolyzed, requires an HPLC method that measures both I and the thiazide. My recommendation is that all thiazide obtained from urine be converted to I and that I be measured by an HPLC method to give maximum precision and sensitivity.

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