Comparison of *In Vitro* Dissolution and *In Vivo* Bioavailability of Methaqualone Tablets in Humans

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Abstract □ Two methaqualone tablets that exhibited different *in vitro* dissolution rates were administered to 11 normal healthy male volunteers. Serial blood samples were withdrawn following administration of each tablet, and plasma methaqualone concentrations were determined by an established spectrophotofluorometric assay. Both tablets produced virtually identical plasma concentration *versus* time profiles in humans, and no statistically significant differences in either the rate or extent of drug absorbed were detected. The results indicate that there is no correlation between *in vivo* bioavailability and the modified NF *in vitro* dissolution test used.

Keyphrases □ Methaqualone—two tablets, *in vitro* dissolution compared to *in vivo* bioavailability in humans □ Dissolution, *in vitro*—methaqualone, two tablets, compared to *in vivo* bioavailability in humans □ Bioavailability, *in vivo*—methaqualone, two tablets in humans, compared to *in vitro* dissolution □ Hypnotic-sedatives—methaqualone, two tablets, *in vitro* dissolution compared to *in vivo* bioavailability in humans

Methaqualone [2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone], a sedative-hypnotic (1), is very slightly soluble in water (2). In humans, it is metabolized by the liver and excreted in the urine and feces (3, 4). Peak plasma concentrations of methaqualone are achieved 1.5–3 hr after oral administration of most tablet dosage forms (5–8). Following administration of 300-mg methaqualone tablets, peak plasma concentrations of about 3.0 μg/ml have been achieved (6, 7).

In recent *in vitro* dissolution rate studies using a modified NF dissolution rate procedure, several lots of methaqualone tablets[1] did not meet existing dissolution rate specifications. These tablets had been aged at room temperature for approximately 2 years. Chemburkar *et al.* (8) previously reported that the standard dissolution rate testing procedures might not correlate with the *in vivo* performance of methaqualone tablets. Therefore, the study reported here was undertaken to substantiate these findings for the particular formulation. More importantly, if present compendial dissolution rate standards cannot be correlated with the *in vivo* bioavailability of methaqualone tablets, the tests probably should be revised.

EXPERIMENTAL

In a two-way crossover study, 11 healthy, nonobese male subjects[2], 20–28 years old and 61–89 kg (mean 71 kg), were randomly selected by sequential admission. The subjects were instructed not to consume any drugs (including enzyme inducers) for at least 30 days preceding the study or alcoholic beverages during the entire study.

One methaqualone tablet (A or B) was given together with 240 ml of water in the morning after an overnight fast (12 hr). The subjects were allowed a standard diet 4 hr following drug ingestion. Blood samples, 8 ml, were obtained in heparinized syringes just prior to drug administration (0 hr) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hr after drug ingestion.

[1] Sopor, Arnar-Stone Laboratories, McGaw Park, Ill.
[2] All subjects were paid and signed a written consent form.

Table I—Dissolution Rate of Methaqualone Tablets

Tablet	Tablet Content, mg of Methaqualone	Dissolution Rate, % per 20 min	Dissolution Rate, % per 30 min
A	303	65.4	98.2
B	304	39.0	53.9
NF specifications		70.0	—

Plasma was immediately separated and frozen until assayed. A washout period of 1 week was allowed between the two treatment phases.

Concentrations of methaqualone in plasma were determined in duplicate by a spectrophotofluorometric procedure (9). A comparison of the spectrophotofluorometric procedure with GLC showed very low plasma concentrations of circulating metabolites of methaqualone during multiple-dose regimens (7). Therefore, the spectrophotofluorometric method was sufficiently specific for methaqualone for single-dose bioavailability studies (7). In this study, each concentration of methaqualone in plasma was corrected for the blank concentration of the 0-hr sample. For the analysis of variance test, a statistical package (10) was used to detect the significance of several sources of variability at the 0.05 level.

The dissolution test was done with the NF rotating-basket assembly set at 100 rpm, using 900 ml of dilute hydrochloric acid (17 ml of concentrated hydrochloric acid/2000 ml of aqueous solution) at 37°. This method is similar to the Method I dissolution test of the NF (2), except that the hydrochloric acid concentration in the NF test is 1/2000. Dissolution data for the methaqualone tablets tested in this study are shown in Table I.

RESULTS AND DISCUSSION

Table II lists the average plasma concentrations found for the two methaqualone tablets after oral administration to 11 fasted volunteers. There were no statistically significant differences in plasma concentrations (as determined by analysis of variance) at any sampling time following Tablets A and B. Likewise, no statistically significant differences in peak plasma concentration, time of peak plasma concentrations, and area under the plasma concentration–time curve (*AUC*) between 0 and 24 hr were found for the two tablets.

An additional important factor in any bioavailability study is the variability in plasma concentrations associated with any given drug treatment. The magnitude of the standard deviations associated with each mean value was comparable for both tablets (Table II). Furthermore, the subject population tested was sufficient to detect at least a 25% difference between treatment means for peak concentration and *AUC* at the 5% significance level with 95% certainty if such differences existed ($\alpha = 0.05$ and $\beta = 0.05$). Therefore, the power of the test was within established standards for bioavailability testing.

No significant trends were associated with the period and subject effects. Statistically significant differences among subjects (intersubject variability) are quite common to most bioavailability studies, and the effects noted for the 4–16-hr sampling time and the 0–24-hr *AUC* are to be expected.

Because of the usual subject population and study condition differences, it serves no useful purpose to attempt to demonstrate exact numerical correlation with reported plasma level data. Nonetheless, the general magnitude of the numbers found in this study was consistent with previous reports. For a 300-mg dose, peak concentrations of 3 μg/ml at 1.5–2 hr have been obtained generally (6, 7). The *AUC* (0–24 hr) obtained for Tablets A and B was, however, higher than a previously reported *AUC* (0–24 hr) value of 26.7 μg/ml × hr (7). Unless a common lot of drug or reference solutions is tested by both laboratories, no absolute conclusions can be drawn from these comparisons.

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Table II—Mean Individual Plasma Concentration Parameters for Methaqualone and Analysis of Variance for Each Indicated Parameter

Hours	Plasma Concentration, μg/ml (Mean ± SD)[a] Tablet A	Tablet B	Statistical Significance[b] Treatment Effect	Period Effect	Subject Effect
0.5	1.27 ± 1.27	1.35 ± 0.936	NS	NS	NS
1.0	3.10 ± 1.05	3.30 ± 1.09	NS	NS	NS
2.0	3.52 ± 0.863	3.29 ± 0.552	NS	NS	NS
3.0	2.93 ± 0.647	2.78 ± 0.572	NS	NS	NS
4.0	2.36 ± 0.575	2.30 ± 0.480	NS	NS	0.05
6.0	1.64 ± 0.366	1.59 ± 0.369	NS	NS	0.01
8.0	1.39 ± 0.287	1.43 ± 0.378	NS	NS	0.05
12.0	1.14 ± 0.265	1.17 ± 0.354	NS	NS	0.05
16.0	1.04 ± 0.279	1.02 ± 0.289	NS	0.05	0.05
24.0	0.848 ± 0.214	0.815 ± 0.253	NS	NS	NS
Peak concentration[c]	3.97 ± 0.718	3.70 ± 0.664	NS	NS	NS
Peak time, hr	1.82 ± 0.750	1.36 ± 0.664	NS	NS	NS
AUC[cd], (μg hr)/ml	34.6 ± 6.17	34.2 ± 8.00	NS	NS	0.05

[a] Average of 11 subjects. [b] A statistical package (10) was used to detect the significance of the factors at the 0.05 level. [c] A difference of 25% in overall means can be detected with $\alpha = 0.05$ and $\beta = 0.05$. [d] Area under plasma concentration–time curve from 0 to 24 hr.

The two methaqualone tablets tested in this study were bioequivalent. Thus, the currently used dissolution test did not accurately reflect the *in vivo* performance of methaqualone tablets. Since a dissolution test serves no useful purpose unless it reflects the potential safety or efficacy of a drug product, this study indicates that a new testing procedure is required.

Both tablets did not meet the existing NF dissolution rate standard (Table I). However, Tablet A could readily be considered an appropriate reference standard since the product met all NDA specifications. Furthermore, the data clearly show that changes of more than 50% in the *in vitro* dissolution rate of a tablet dosage form produced no apparent significant effect *in vivo*. Additionally, Chemburkar *et al.* (8) indicated that the dissolution rate test that most closely correlated with *in vivo* bioavailability was an extremely slow 2-rpm procedure. Based on their report plus the findings in this paper, serious considerations should be given toward revision of the current NF dissolution rate standards for methaqualone tablets.

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Binding of Drugs to Ion-Exchange Resins in Simulated Gastric Fluid

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Abstract □ The binding of 13 frequently abused drugs to two ion-exchange resins was studied in simulated gastric fluid. The results were compared with those previously obtained with activated charcoal as the adsorbent. The ion-exchange resins adsorbed the drugs more slowly than activated charcoal, and the binding capacities of the resins were inferior. These ion-exchange resins are unlikely to be very useful in removing drugs from the stomach.

Keyphrases □ Binding—various drugs to two ion-exchange resins in simulated gastric fluid, compared to previous results with charcoal □ Ion-exchange resins—binding of various drugs in simulated gastric fluid, compared to previous results with charcoal □ Adsorption—various drugs to two ion-exchange resins in simulated gastric fluid, compared to previous results with charcoal

The effective removal of drugs from the blood of animals and humans by hemoperfusion is well established (1). In the early work, use was made of the irreversible binding of drugs to activated charcoal by nonspecific surface adsorption. Charcoal hemoperfusion is not currently employed, however, since Hagstram *et al.* (2) documented platelet adsorption and the release of particles of charcoal into blood. More recently, coated activated charcoal (3)

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