

# Mechanism of Interaction between Polyols and Aluminum Hydroxide Gel

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**Abstract** □ IR spectroscopy and changes in the rate of acid neutralization were used to study the interaction between various polyols and aluminum hydroxide. Hydrogen bonding is responsible for this interaction, although structural requirements limit the polyols that interact with aluminum hydroxide. Mannitol and sorbitol, both linear polyols, interacted with sulfate-containing aluminum hydroxide gel and aluminum hydroxycarbonate gel, while inositol, a cyclic polyol, did not interact. The adsorbed polyol has the favorable effect of inhibiting the polymerization reaction that occurs on aging and the negative effect of reducing the rate of acid neutralization. Thus, the specific polyol and concentration must be carefully selected to maximize the desired effect of stabilizing the gel structure. The presence of mannitol in the reaction medium during precipitation did not significantly enhance gel structure stability, probably because the mannitol was desorbed during the washing process as a consequence of the weak adsorption forces.

**Keyphrases** □ Aluminum hydroxide—mechanism of interaction with polyols □ Polyols—mechanism of interaction with aluminum hydroxide □ Spectroscopy, IR—mechanism of interaction between polyols and aluminum hydroxide gel □ Structure stability—mechanism of interaction between polyols and aluminum hydroxide gel

The use of a polyol such as sorbitol to improve the stability of aluminum hydroxide antacid formulations, a widely followed practice, has been the object of numerous studies and patents (1–8). Although these reports demonstrated the beneficial effects of polyols, the molecular basis of the interaction has not been described. This study examined the mechanism of interaction between polyols and aluminum hydroxide gel and the factors that affect the optimum use of polyols in antacid formulations.

## EXPERIMENTAL

Aluminum hydroxycarbonate gel was obtained commercially. A sulfate-containing aluminum hydroxide gel containing 3.4% equivalent aluminum oxide (0.33 M) was precipitated by the reaction of aluminum sulfate and strong ammonia solution NF (NF XV) (9). To determine the effect of the presence of mannitol at the time of precipitation, a series of precipitations of a sulfate-containing aluminum hydroxide gel containing 1.5% equivalent aluminum oxide (0.147 M) was carried out as described but with either 0.22 or 0.588 M mannitol dissolved in the aluminum sulfate solution prior to precipitation. The sulfate-containing aluminum hydroxide gel was divided into two portions. One portion was washed in the usual manner with three volumes of deionized water, and the second portion was not washed. The lower concentration of equivalent aluminum oxide was required due to the limited solubility of mannitol (0.99 M in water) (10).

The ease of mannitol desorption from the sulfate-containing aluminum hydroxide gel was determined by preparing a suspension containing 0.22 M mannitol and 0.147 M equivalent aluminum oxide. The mixture was centrifuged at 15,000 rpm (27,000×g) for 30 min. The clear supernate was decanted, weighed, and assayed for mannitol by a microcolorimetric method (11). The solid phase was resuspended in double-distilled water to the original volume, and the procedure was repeated five times.

Sorbitol, mannitol, and inositol were selected for the IR study because each is a six-carbon polyol containing one hydroxide per carbon. Sorbitol and mannitol are linear, while inositol is cyclic. The deuteration procedure of Hamill and Freudenberg (12) was adopted since the polyols are water soluble, nonvolatile, and stable in aqueous solution up to 100°. Deuterium oxide (30 g) was added to 5 g of polyol, and the solution was

maintained at 70° for 72 hr followed by lyophilization<sup>1</sup>. The preparation of deuterated sorbitol was not successful since a glass was always obtained during lyophilization (13). The IR spectra of the deuterated mannitol and deuterated inositol were compared to those of mannitol and inositol. The OH:OD frequency ratio was 1.35 for each hydroxyl band, which confirmed that deuteration had occurred (14).

The interaction between the deuterated polyols and aluminum hydroxycarbonate gel or sulfate-containing aluminum hydroxide gel was studied by preparing a suspension containing 0.50 M deuterated polyol and 0.33 M equivalent aluminum oxide. The suspensions were allowed to mix for 1 hr, and a sample was air dried. IR spectra were recorded<sup>2</sup> using potassium bromide pellets (1 mg of sample/300 mg of potassium bromide). The positions of the hydroxy and deuterio stretching bands were determined using an abscissa expansion of 5× with a wave number marker at every 10 cm<sup>-1</sup> and an ordinate expansion of either 1× or 10×.

The rate of acid neutralization of suspensions containing 0.50 M polyol and 0.33 M equivalent aluminum oxide was determined by pH-stat titration<sup>3</sup> at pH 3.0 and 25° (15) during aging at 40°. The effect of polyol concentration on the rate of acid neutralization was studied by determining the pH-stat titrations of a series of suspensions containing 0.098 M equivalent aluminum oxide and varying molar ratios of polyol. The lower concentration of equivalent aluminum oxide was necessary due to the low solubility of inositol (0.78 M) (10).

The soluble aluminum content of aluminum hydroxycarbonate gels containing various amounts of mannitol was determined by centrifugation at 15,000 rpm (27,000×g) for 30 min and measurement of the aluminum content of the supernate by atomic absorption spectroscopy<sup>4</sup> (16).

## RESULTS AND DISCUSSION

Amphoteric compounds such as aluminum hydroxide usually exhibit hydroxyl stretching frequencies at 3660–2900 cm<sup>-1</sup> (17). The hydroxyl stretching frequencies of polyols occur at 3450–3200 cm<sup>-1</sup> (18). An interaction between aluminum hydroxide and a polyol that involves the hydroxyls of either the aluminum hydroxide or the polyol would be difficult to study by IR spectroscopy because the hydroxyl stretching frequencies overlap. This problem is aggravated by the occurrence of hydroxyl stretching vibrations of adsorbed water in the same region. However, the interaction between deuterated polyols and aluminum hydroxide can be directly studied by IR spectroscopy since deuterio stretching frequencies of deuterated polyols occur between 2550 and 2370 cm<sup>-1</sup>. Aluminum hydroxide does not exhibit any IR absorption bands in the 2600–2400-cm<sup>-1</sup> region. There appears to be no hydrogen–deuterium exchange between the deuterated polyols and the aluminum hydroxycarbonate gel at these experimental temperatures. Since the preparation of the potassium bromide pellets required air drying the sample, there is the question of whether the dehydration process changes the apparent nature of the interaction. The fact that no shift was observed for the inositol–aluminum hydroxide systems suggests that the shifts observed for mannitol were not an artifact.

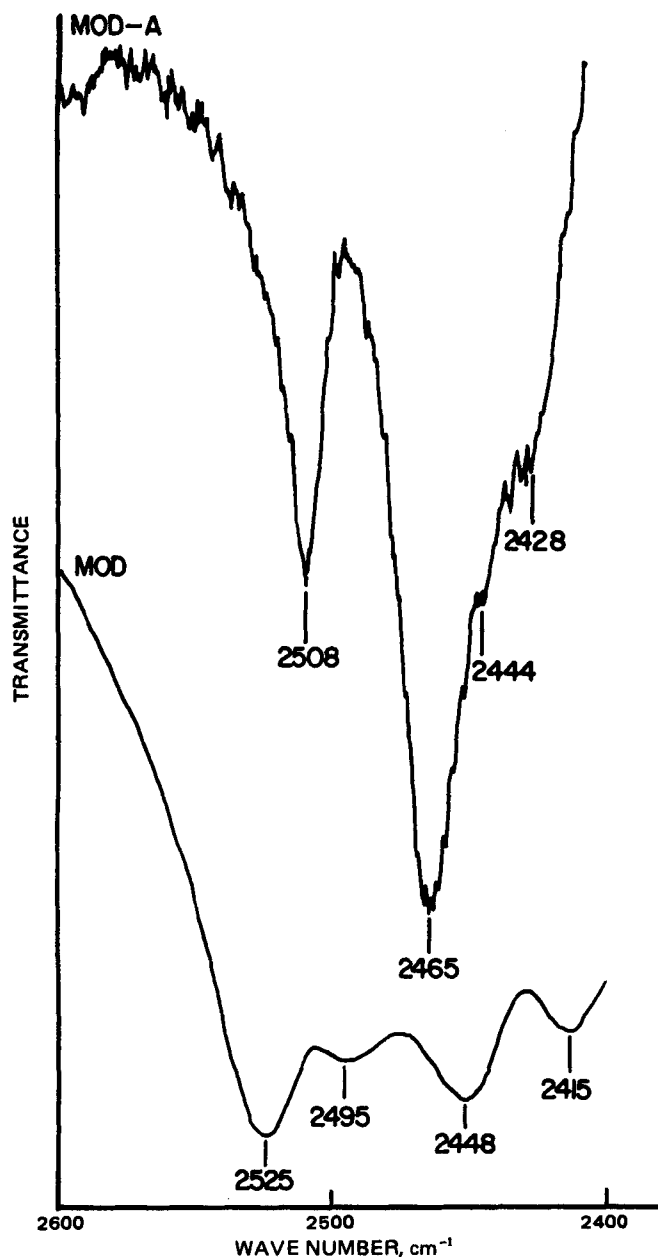
Figure 1 shows that both the frequency and relative intensity of the deuterio stretching bands of deuterated mannitol are significantly altered by the aluminum hydroxycarbonate gel. The free deuterio band of deuterated mannitol occurred at the highest frequency, i.e., 2525 cm<sup>-1</sup>, and the intermolecularly bonded deuterio peaks occurred at the lower frequencies, i.e., 2495, 2448, and 2415 cm<sup>-1</sup> (19, 20). Adsorption of deu-

<sup>1</sup> Virtis Research Equipment, Gardiner, N.Y.

<sup>2</sup> Model 180, Perkin-Elmer Co., Norwalk, Conn.

<sup>3</sup> PHM 26, TTT 11, ABU 12 (2.5 ml), TTA 3, and SBR 2, Radiometer, Copenhagen, Denmark.

<sup>4</sup> Model 290B, Perkin-Elmer Co., Norwalk, Conn.

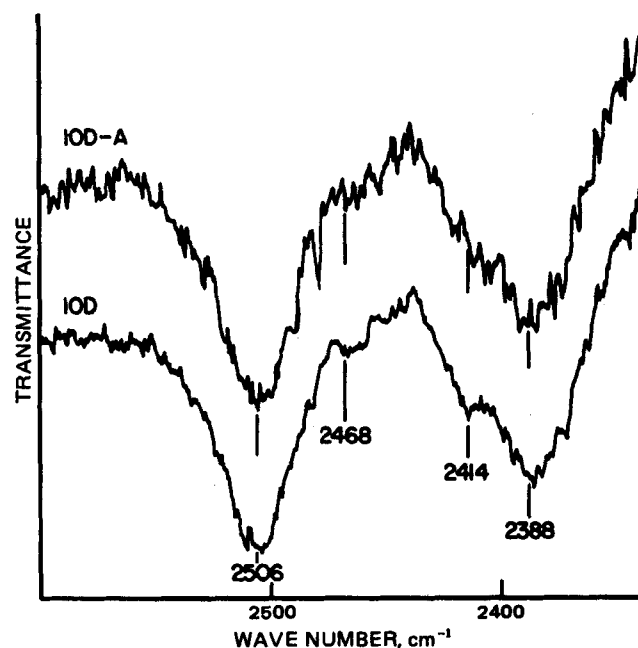


**Figure 1**—Deuterioxy stretching bands of deuterated mannitol (MOD) and deuterated mannitol in the presence of aluminum hydroxycarbonate gel (MOD-A). Ordinate expansion is 1X for MOD and 10X for MOD-A.

terated mannitol by aluminum hydroxycarbonate gel as a consequence of hydrogen bonding would be expected to cause the free deuterioxy band to shift to a lower frequency, as observed in Fig. 1. The band at 2525  $\text{cm}^{-1}$  shifted to 2508  $\text{cm}^{-1}$ , which suggests weak hydrogen bonding. However, the bands arising from intermolecular hydrogen bonds would be expected to shift to higher frequencies when monolayer adsorption occurs. From Fig. 1, it appears that the major intermolecular vibration at 2448  $\text{cm}^{-1}$  shifted upward to 2465  $\text{cm}^{-1}$  and that the 2415 band shifted to appear as a shoulder in the 2430- $\text{cm}^{-1}$  region of the deuterated mannitol-aluminum hydroxycarbonate gel system. Thus, the complex changes observed in the IR spectrum of deuterated mannitol in the presence of aluminum hydroxycarbonate gel reflect the adsorption of deuterated mannitol onto the aluminum hydroxycarbonate surface.

A similar change in the IR spectrum of deuterated mannitol occurred in the presence of sulfate-containing aluminum hydroxide gel with the deuterioxy stretching bands appearing at 2516, 2476, 2450, and 2414  $\text{cm}^{-1}$  as a consequence of adsorption.

The carbonate stretching bands of aluminum hydroxycarbonate at 1521 and 1467  $\text{cm}^{-1}$  were not affected by the presence of deuterated mannitol, suggesting that the coordinated carbonate is not involved in



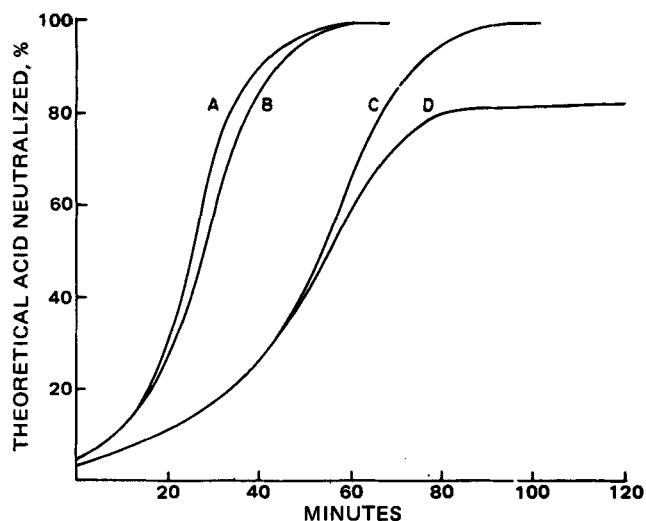
**Figure 2**—Deuterioxy stretching bands of deuterated inositol (IOD) and deuterated inositol in the presence of aluminum hydroxycarbonate gel (IOD-A). Ordinate expansion is 10X.

the interaction with mannitol. However, the sulfate stretching frequency of the sulfate-containing aluminum hydroxide gel shifted from 1130 to 1110  $\text{cm}^{-1}$  in the presence of deuterated mannitol. IR evidence indicates that carbonate is strongly coordinated to aluminum in aluminum hydroxycarbonate gel while sulfate is weakly coordinated to aluminum in sulfate-containing aluminum hydroxide gel (21). The apparent absence of interaction of deuterated mannitol with coordinated carbonate in aluminum hydroxycarbonate gel may be due to the strong coordination of carbonate to aluminum, which would not be substantially affected by hydrogen bonding with deuterated mannitol. The weaker sulfate-aluminum bond in sulfate-containing aluminum hydroxide gel is affected by hydrogen bonding with deuterated mannitol, and a 20  $\text{cm}^{-1}$ -shift in the frequency of the sulfate bond was observed.

The hypothesis that the interaction between mannitol and aluminum hydroxide is due to hydrogen bonding is further supported by the observation that the soluble aluminum content of aluminum hydroxycarbonate gel was 0.3% and did not change when mannitol was added to the gel in a molar ratio of 0.5-4 M mannitol per equivalent aluminum oxide. Thus, the interaction between mannitol and aluminum hydroxycarbonate gel is not strong enough to solubilize aluminum.

The IR spectrum of deuterated inositol was not affected by the aluminum hydroxycarbonate gel (Fig. 2), thus indicating that no interaction occurs between inositol and aluminum hydroxide. However, the deuterioxy stretching frequencies of deuterated inositol (2506, 2468, 2414, and 2388  $\text{cm}^{-1}$ ) were all lower than those observed for deuterated mannitol (2525, 2495, 2448, and 2415  $\text{cm}^{-1}$ ). Thus, intermolecular association of inositol is expected to be greater than for mannitol.

IR evidence for the interaction of mannitol with aluminum hydroxide gel and the absence of an interaction with inositol is supported by the change in acid reactivity of mixtures of aluminum hydroxycarbonate gel and polyols during aging. The pH-stat titrations of the aluminum hydroxycarbonate gel (0.33 M equivalent aluminum oxide) and mixtures of the aluminum hydroxycarbonate gel containing 0.5 M mannitol, sorbitol, or inositol showed that all four samples reacted completely in ~60 min (Fig. 3), although the rate of acid neutralization was slightly slower in the mixtures containing sorbitol or mannitol. The pH-stat titrations of the aluminum hydroxycarbonate gel and the inositol-containing mixture were significantly affected by aging at 40° for 1 week. As seen in Fig. 3, ~20% of the aluminum hydroxycarbonate gel reacted very slowly at pH 3, suggesting that extensive polymerization of the aluminum hydroxy polymers had occurred (22). In contrast, the mixtures containing mannitol or sorbitol reacted completely after aging at 40° for 1 week, although the reaction rate decreased, requiring 90 min for complete neutralization. Thus, sorbitol and mannitol were effective in minimizing polymerization in aluminum hydroxycarbonate gel while inositol did not show any effect on the structural changes during aging.



**Figure 3**—Effect of polyols on the rate of acid neutralization of aluminum hydroxycarbonate gel (AHC). Key: A, initial pH-stat titration of AHC and inositol-containing AHC; B, initial pH-stat titration of sorbitol-containing AHC and mannitol-containing AHC; C, 1 week, 40° titration of sorbitol-containing AHC and mannitol-containing AHC; and D, 1 week, 40° titration of AHC and inositol-containing AHC.

Therefore, the hydrogen bonding of polyols with aluminum hydroxide is an important reaction because the adsorbed polyol appears to interfere with the polymerization reaction and, consequently, the structural changes that ultimately lead to the inactive crystalline forms of aluminum hydroxide are minimized. However, the reaction between polyols and aluminum hydroxide gel is not universal. The difference in the effect of mannitol and sorbitol in comparison to inositol may be due to differences in the conformation of the polyol or in the strength of its intermolecular forces. Mannitol and sorbitol are both linear polyols, while inositol is related to cyclohexane. A linear conformation may permit more extensive hydrogen bonding to the aluminum hydroxide surface than is possible with cyclic polyols because of steric factors and the position of hydrogen

**Table I**—Effect of Polyols on the Rate of Acid Neutralization of Aluminum Hydroxycarbonate Gel Containing 0.98 M Equivalent Aluminum Oxide

Polyol Added	$T_{50}$ , min			
	0.3 M polyol	1.3 M polyol	2.3 M polyol	3.3 M polyol
Control <sup>a</sup>	26	26	26	26
Mannitol	26	28	30	44
Sorbitol	26	28	30	44
Inositol	26	26	26	26

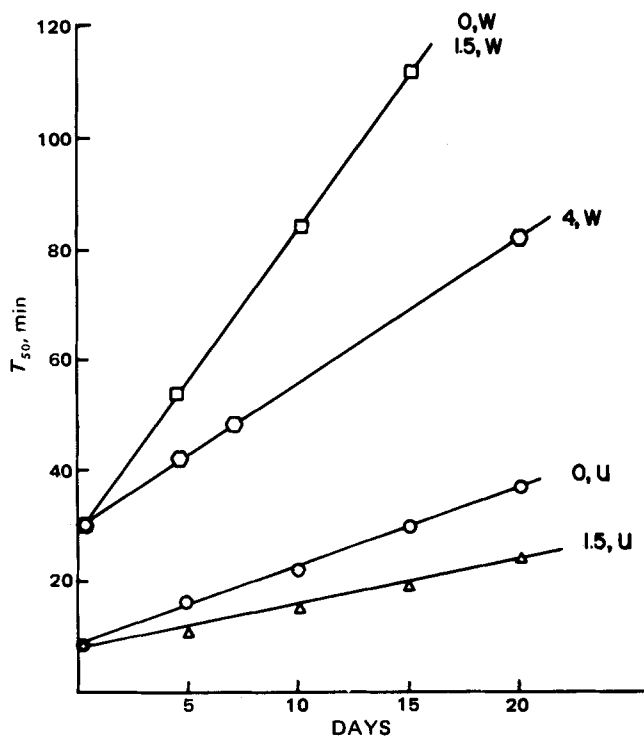
<sup>a</sup> Aluminum hydroxycarbonate gel.

bonding sites. The melting points of sorbitol, mannitol, and inositol are 110, 168, and 225°, respectively (10). The higher melting point and lower deuterioxy-stretching frequencies of inositol suggest the presence of strong intermolecular forces. Thus, the tendency of inositol toward self-association may be greater than the tendency toward adsorption by aluminum hydroxide.

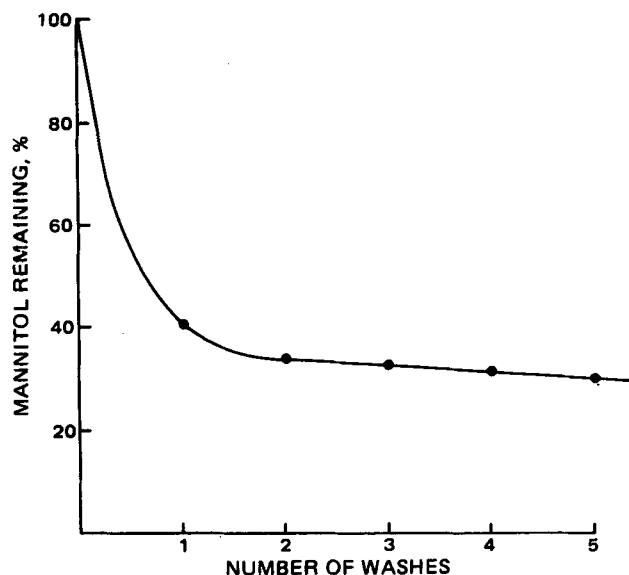
The polyol concentration used to stabilize aluminum hydroxide must be carefully selected because the adsorbed polyol, in addition to interfering with polymerization, may also slow the rate of reaction with protons and thus reduce the rate of acid neutralization. Evidence of this effect was seen (Fig. 3) as a slight reduction in the rate of acid neutralization occurred when sorbitol or mannitol was added to the aluminum hydroxycarbonate gel. This effect is seen clearly in Table I where the rate of acid neutralization of aluminum hydroxycarbonate gel, as measured by the time required to neutralize 50% of the sample ( $T_{50}$ ), increases in direct relationship to the concentration of mannitol or sorbitol. In the presence of high levels of mannitol or sorbitol, the  $T_{50}$  increased from 26 to 44 min. In contrast, inositol did not affect the rate of acid neutralization.

Since changes in the aluminum hydroxide gel structure occur most rapidly immediately after precipitation (23), it may be advisable to incorporate a polyol in the reaction medium to achieve the maximum rate of acid neutralization. Thus, a sulfate-containing aluminum hydroxide gel was precipitated in the presence of varying amounts of mannitol. As seen in Fig. 4, the sulfate-containing aluminum hydroxide gel precipitated in the presence of a molar ratio of 1.5 M mannitol per equivalent aluminum oxide aged at the same rate as the control. However, the rate of loss of acid reactivity was substantially reduced when the sulfate-containing aluminum hydroxide gel was precipitated in the presence of a molar ratio of 4 M mannitol per equivalent aluminum oxide.

It was hypothesized, based on the hydrogen bonding mechanism indicated by the IR study, that the washing procedure removed most of the mannitol, and this hypothesis is supported by the desorption profile shown in Fig. 5. Most of the mannitol was removed by the first volume of wash water, and only ~30% of the added mannitol remained after the described washing procedure. The rate of acid neutralization of the unwashed sulfate-containing aluminum hydroxide gel was much greater



**Figure 4**—Change in the rate of acid neutralization during aging at 25° of sulfate-containing aluminum hydroxide gels precipitated in the presence of 0, 1.5, and 4 M mannitol per equivalent aluminum oxide. Key: W, washed; and U, unwashed.



**Figure 5**—Desorption of mannitol during washing with distilled water.

than that of the washed portion, and the rate of loss of acid reactivity during aging was also reduced. This behavior confirms the strong stabilizing effect of anions (23). However, the unwashed portion that was precipitated in the presence of a molar ratio of 1.5 M mannitol per equivalent aluminum oxide showed the smallest decrease in the rate of acid neutralization during aging. The interaction between polyols and aluminum hydroxide gel apparently is too weak to recommend the incorporation of mannitol or sorbitol in the reaction medium. However, the results suggest the addition of mannitol or sorbitol immediately after washing.

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# Effect of Age and Gender on Disposition of Temazepam

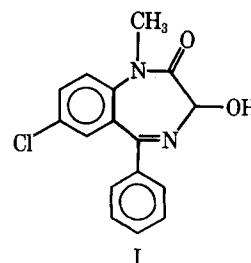
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**Abstract** □ Thirty-two male and female volunteers, 24-84 years of age, ingested single 30-mg doses of temazepam, a 3-hydroxy-1,4-benzodiazepine derivative used as a hypnotic agent. Kinetics of total and unbound temazepam were determined from multiple plasma temazepam concentrations measured during 48 hr after the dose. The temazepam elimination half-life ranged from 8 to 38 hr and was longer in women than in men (16.8 versus 12.3 hr,  $p < 0.05$ ). Likewise, clearance of total temazepam (assuming complete absorption) was higher in men than in women (1.35 versus 1.02 ml/min/kg,  $p < 0.025$ ). Neither half-life nor clearance was significantly related to age. The volume of distribution of total temazepam (mean 1.40 liters/kg) was unrelated to age or gender. Temazepam was extensively protein bound, with a mean free fraction of 2.6% (range 1.7-3.4%). The free fraction increased with age ( $r = 0.45$ ,  $p = 0.01$ ), partly due to the inverse relation of the free fraction to plasma albumin concentration ( $r = -0.34$ ,  $p = 0.06$ ) and the age-related decline in plasma albumin ( $r = -0.49$ ,  $p < 0.005$ ). After correction for individual differences in binding, clearance of unbound temazepam in men was higher than in women (50.5 versus 39.7 ml/min/kg,  $0.05 < p < 0.1$ ), and it tended to decline with age in both sexes ( $r = -0.44$  and  $-0.43$ , respectively,  $p = 0.1$ ).

**Keyphrases** □ Temazepam—effect of age and gender on disposition and elimination □ Tranquilizers—temazepam, effect of age and gender on disposition and elimination □ Hypnotics—temazepam, effect of age and gender on disposition and elimination

Temazepam (I) is a 3-hydroxy-1,4-benzodiazepine derivative used as a hypnotic agent. The major metabolic pathway of temazepam in humans involves conjugation



with glucuronic acid at position 3, yielding a water-soluble glucuronide metabolite that is excreted in the urine (1). Since the aging process may alter drug pharmacokinetics, this study was undertaken to assess the disposition and elimination of temazepam in young and elderly volunteers.

## EXPERIMENTAL

**Subjects**—Thirty-two healthy male and female volunteers, 24-84 years of age, participated after giving written informed consent. They were divided into four groups of young male, young female, elderly male, and elderly female subjects (Table I). All young subjects were free of any identifiable medical disease and were taking no medications. Elderly individuals were ambulatory, active, and in general good health. Five elderly subjects were taking medications for the treatment of cardiovascular disease that was clinically stable and compensated.