Comparison of Urological Irrigating Fluids Containing Glycine and Mannitol in Volunteers

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BACKGROUND. We compared symptoms and indices of fluid distribution after experimental administration of glycine and mannitol solutions, since these irrigating fluids are sometimes absorbed by the patient during genitourinary surgery.
METHODS. Glycine 1.5% and mannitol 3%, both with ethanol 1% added, were given by intravenous infusion at a rate of 0.5 ml/kg/min during 30 min to 12 male volunteers. Symptoms, cognitive status, hemodynamics, electrocardiogram during 24 hr, computerized tomography of the brain, bioimpedance, blood chemistry, and breath ethanol concentrations were recorded.
RESULTS. Glycine was associated with more symptoms than mannitol ($P < 0.006$), but the cognitive status, computerized tomography examinations, electrocardiograms, and breath ethanol concentrations did not differ between the solutions. The urinary excretion of fluid and sodium was greater after mannitol ($P < 0.04$), while only the glycine infusions hydrated the cells ($P < 0.05$). For both fluids, the intravascular and interstitial volumes were below baseline 3 hr after the experiment started ($P < 0.01$).
CONCLUSIONS. Glycine 1.5% had a higher tendency than mannitol 3% to cause symptoms and to accumulate in the cells. *Prostate 41:89–98, 1999.*

KEY WORDS: **ethyl alcohol; complications of irrigation; glycine; mannitol**

INTRODUCTION

An irrigating fluid is routinely used in transurethral resection of the prostate (TURP) to clear the operating field of blood and pieces of prostatic tissue. It has been known for 50 years that symptoms often arise and that death may ensue when such irrigating fluids are absorbed by the patient [1]. However, there are differences between the fluids with respect to the profile of adverse effects. The irrigating fluids used in the clinic consist of electrolyte-free water containing glycine, mannitol, or sorbitol and, in some countries, a small amount of ethanol. We previously found that glycine 1.5% is associated with more neurological symptoms than mannitol 3% when absorbed during TURP [2]. Furthermore, animal studies show that intravenous infusion of glycine is followed by more tissue damage [3] and a higher mortality [3,4] than with mannitol solution. The reasons for these differences are not well-understood.

To evaluate possible differences in the adverse effects profile and the body's handling of these two widely used irrigating fluids in humans, we administered moderate amounts of them (average 1,250 ml) by intravenous infusion to healthy volunteers and studied symptoms, cognitive status, electrocardiogram, hemodynamics, and the distribution of the volume load. The solutions had a similar osmolality and both contained ethanol 1%, which is used in our clinics because it allows early detection quantification of fluid absorption by means of expired-breath tests [5].

SUBJECTS AND METHODS

Twelve healthy male volunteers aged between 22–35 (median, 28) years and with a body weight of 73–

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98 (median, 83) kg were recruited for the investigation. Exclusion criteria were smoking and/or living in a house with radon gas levels above the nationally acceptable limit (400 Bq/m^2). The study was approved by the local Ethics and Isotope Committees.

Each volunteer received, in random order and separated by at least 10 days, an intravenous infusion of glycine 1.5% plus ethanol 1% and, on the other occasion, mannitol 3% plus ethanol 1% (Baxter Healthcare, Thetford, UK). The osmolality of these fluids was 430 and 400 mosmol/kg, respectively, and the pH was 6.0.

Procedure

The subjects had a light breakfast at home and were not allowed to eat or drink during the experiments. They had five electrodes placed on the chest for continuous recording of the electrocardiogram, and underwent computerized tomography of the brain. Thereafter, cannulas were placed in the antecubital veins of both arms for blood sampling and infusion of irrigating fluid, respectively. After resting 20 min to reach hemodynamic steady state, infusions were given at a constant rate of 0.5 ml/kg/min over 30 min with the aid of two infusion pumps (Flo-Gard 6201, Baxter Healthcare, Deerfield, IL). All volunteers underwent a second computerized tomography of the brain 4 hr after starting the infusion (range, 3.0–4.9 hr).

Symptoms and Mental Status Testing

Symptoms and signs of adverse effects were noted during and after the infusions. The volunteers were also asked to report any feeling of uneasiness on the morning after the experiment. Symptoms were evaluated according to a scoring system: headache, vertigo, tiredness, and dyspnea (mild = score of 1, more severe = score of 2), fainting (score of 2), and prolonged complaints of prickling or heat sensations (score of 1).

Cognitive function was examined using a questionnaire ("mini-mental status") just before and 1 and 3 hr after starting the infusion [6,7]. This test, which is considered to be reliable even when repeated, covers orientation, attention, recall, calculation, and language, and takes about 5 min to complete. The maximum score is 30. To avoid excessively high scores due to a recall effect, 7 of the 11 questions were modified in both the second and the third mini-mental status test during the same experiment, but the same questionnaires were used in the two experiments.

Hemodynamics

Blood pressure and heart rate were measured at regular intervals during 3 hr from the start of the infusion with an automatic digital monitor (Hewlett Packard M 1008 A or M 1020 A, Hewlett-Packard, Böblingen, Germany).

The long-term recordings of the electrocardiogram were made using a cassette-based two-channel recorder (Sherpa, Reynolds Medical, Hertford, UK). Electrode positions similar to V_1 and V_5 were used. The volunteers were monitored for 24 hr. The signal was digitalized and stored using a PC-based system (Aspect Holter System, Daltek, Borlänge, Sweden) for later data-analysis with respect to rhythm, incidence of supraventricular and ventricular arrhythmias, and aberrant QRS complexes. The complete set of recordings was scanned manually for T-wave abnormalities. Using the Holter system, maximum T-wave amplitude was measured beat-to-beat in all recordings.

Computerized Tomography

All computerized tomography examinations of the brain were carried out using GE HiSpeed Advantage equipment (GE Medical Systems, Milwaukee, WI), with continuous transaxial sections parallel to the skull base. Each examination comprised 16–18 sections. The total effective radiation dose for all four examinations in each volunteer was 4.4 mSv; the national effective radiation dose in Sweden is 5 mSv per year. The films were evaluated by three senior radiologists independently of each other. In assessing the presence of edema on a 3-point scale (0 = none, 1 = minor, 2 = pronounced edema) as proposed by Istre et al. [8], attention was paid to the width of the sulci, ventricles, and basal cisterns and also to the discrimination between gray and white matter.

Blood and Breath Sampling

Blood samples were drawn from the venous cannula at 0, 30, 60, and 180 min in each experiment. The blood hemoglobin (B-Hb) concentration was determined using a Technicon H2 (Bayer, Tarrytown, NY) and the serum concentrations of sodium (S-Na) and potassium (S-K) using an Ektachem 950IRC System (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). Serum osmolality was determined by means of an Osmometer 3C2 (Advanced Instruments, Inc., Norwood, MA).

Plasma ammonia was measured by an enzymatic method with a Hitachi 917 (Hitachi Co., Naka, Japan) just before the glycine-ethanol infusion began and again at 60 min. As mannitol is eliminated by urinary excretion and not by metabolism, the plasma ammonia level was not measured after these experiments.

The urinary excretion and the urine concentration

of sodium and potassium were measured just before and at 1 hr and 3 hr after starting the infusion.

The expired breath ethanol concentration was measured every 5 min during the infusions by a portable device, the Alcolmeter S-D2 (Lion Laboratories, Barry, UK). The Alcolmeter was calibrated by administering an alcohol-in-gas standard test gas in the morning before each experiment.

Mathematical Model

The distribution of infused irrigant water between the body fluid compartments was calculated assuming that the extracellular fluid volume makes up 20% of the body weight and corresponds to the distribution volume of sodium. The baseline blood volume was estimated according to a regression equation based on the height and body weight of the subject [9]. The expansion of blood volume was calculated as the product of the baseline blood volume and the hemodilution, with a correction for blood sampling [10]. The diffusion of fluid into the intracellular space was obtained from a comparison between the distribution volume corresponding to the dilution of the serum sodium level and the actual amount of infused fluid and the urinary excretion of water and sodium. The mathematics involved are shown in the Appendix [11].

Bioimpedance

The changes in volume of the fluid compartments in the whole body and in one leg were assessed by Xitron 4000 bioelectrical impedance analysis (Xitron Technologies, Inc., San Diego, CA). Two electrodes were placed on the right wrist, iliac crest, and ankle joint. The bioelectrical analysis involves sending small currents in a series of 50 frequencies between 5–500 kHz through these electrodes [12,13]. The fluid volumes were calculated from the recorded impedance by the computer software delivered with the apparatus, using the baseline body weight for all occasions, while the percentage change in impedance was reported for the leg measurements. The intracellular volume was obtained as the difference between the total body water and the extracellular volume. The subject was supine for at least 15 min before all examinations, which took place before and at 1 hr and 3 hr after starting the infusion. Each reported value represents the mean of three measurements. The coefficients of variations were 0.3% for the extracellular fluid volume and 2.0% for total body water.

Statistics

The results are presented as the mean ± standard deviation or, when there is a skewed distribution, as the median and the 10th and 90th percentiles. Changes were evaluated by repeated-measures analysis of variance (ANOVA), and the comparison with the baseline was made using Dunnett's post hoc test [14]. Differences between fluids were studied by using the paired *t*-test when the data showed a normal distribution, or else by the Wilcoxon matched-pair test. $P < 0.05$ was considered significant.

RESULTS

Symptoms

The glycine experiments were associated with a higher symptom score than the mannitol experiments (median 2.0 vs. 0.5, respectively; Wilcoxon's test, $P < 0.006$) (Fig. 1, top). Tiredness (n = 7), headache (n = 4), and prolonged problems involving prickling sensations in the skin (n = 4) were the most common complaints. One volunteer fainted when rising to give a urinary sample 50 min after the end of the glycine infusion.

The "mini-mental status" test of cognitive function did not show any statistically significant changes during the experiment.

Hemodynamics

The mean arterial pressure did not change in response to the mannitol infusion, while a transient increase, followed by a late decrease, occurred when glycine was infused (Fig. 1, bottom). These changes were mainly due to the systolic pressure, which was significantly below baseline at 3 hr (112 ± 10 mm Hg vs. 119 ± 12 mm Hg; $P < 0.005$). The heart rate tended to decrease during the infusion, but this change was not statistically significant.

The 24-hr electrocardiogram recording showed similar patterns after the mannitol and glycine infusions, and the indices of heart function did not differ significantly from the control recording (Table I). No negative T waves developed. However, the fainting event involving one volunteer after the glycine infusion coincided with asystole lasting 6 sec.

Computerized Tomography of the Brain

Mild cerebral edema was judged to be present by at least one of the radiologists in 9 of the 24 infusion experiments (38%), but in only 3 experiments was such edema reported by more than one radiologist (13%). There was no difference between the fluids in respect to these observations. Pronounced cerebral edema was not observed. There was no correlation

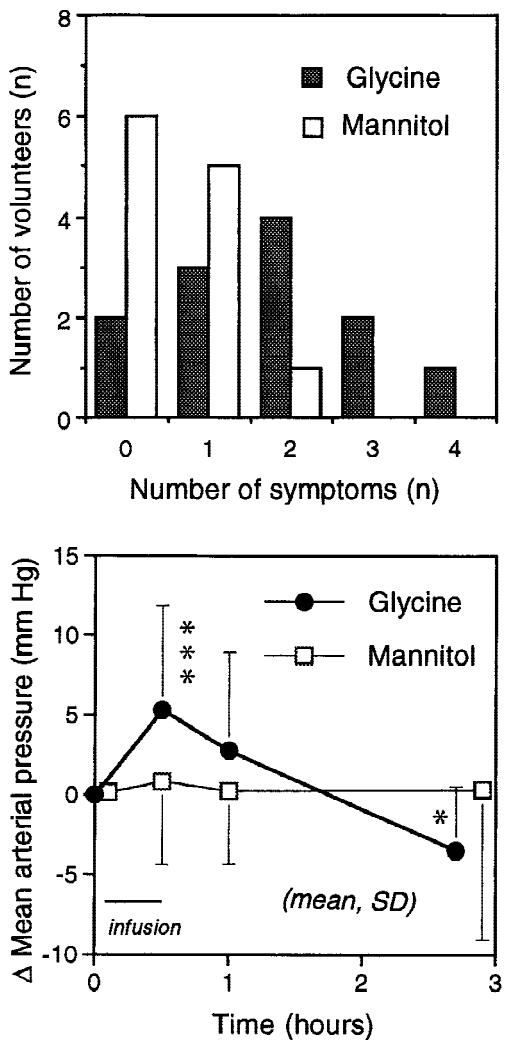

Fig. 1. Number of symptoms (**top**) and the mean arterial pressure (**bottom**) associated with intravenous infusion of 15 ml/kg of glycine 1.5% and mannitol 3%, both with ethanol 1% added, over 30 min in 12 male volunteers. A significant change from baseline level is indicated by $*P < 0.05$ and $***P < 0.001$.

between the symptom score and the results of tomography.

Blood Chemistry

The B-Hb concentration was more reduced at the end of the mannitol infusions than at the end of the glycine infusions (paired *t*-test, $P < 0.03$), but no difference was found at 1 hr and 3 hr (Fig. 2, left). Serum sodium dropped more after the mannitol experiments, a difference that persisted throughout the experiment (repeated-measures ANOVA, $P < 0.012$; Fig. 2, middle). The serum potassium level increased significantly after both infusions, but it increased more after glycine ($P < 0.01$; Fig. 2, right). Serum osmolality also increased after both infusions, from 283 ± 5 to 285 ± 5 mosmol/kg ($P < 0.03$), but baseline levels were already reached at 1 hr.

The median blood ammonia level was 36 μmol/l (24–46) before and 46 μmol/l (22–80) after the glycine infusion ($P < 0.04$). The greatest change, from 47 to 107 μmol/l, occurred in a 27-year-old man with normal liver function tests. He complained of tiredness during and after the infusion.

Breath and Urine

The breath ethanol concentration increased gradually during the infusion, with no difference between the fluids (Fig. 3, left). An estimate of the absorbed volume as determined by the ethanol nomogram (Fig. 4) and the fluid volume actually infused differed by 132 ml (25–313) at 10 min, 146 ml (−44–326) at 20 min, and −38 ml (−230–277) at 30 min during the experiments (Fig. 3, right).

Urinary excretion was higher after mannitol was infused (Table II) and exceeded the infused amount by 535 ml (median, $P < 0.01$). The sodium excretion was also higher after mannitol ($P < 0.04$) and averaged 68 mmol during the 3 hr that urine was collected.

Fluid Distribution

Mathematical model. The baseline blood volume was estimated to be 5.66 ± 0.32 l. The greater decrease in B-Hb at the end of the infusion indicated a more pronounced increase in blood volume during the mannitol experiments ($P < 0.02$), while slight hypovolemia was the end result of both infusion experiments (Fig. 5, left).

The calculated hydration of the interstitial fluid space was greater after the infusion of mannitol than after glycine (pooled data at 1 and 3 hr, $P < 0.03$). For both fluids, the size of the interstitial fluid space was below baseline at 3 hr (Fig. 5, middle).

Glycine significantly increased the volume of the intracellular fluid space at 1 and 3 hr, while no change was found after the mannitol infusions (Fig. 5, right).

Bioimpedance. For both fluids, the extracellular fluid volume was below baseline at 1 and 3 hr (Fig. 6, upper left). Glycine, but not mannitol, increased the intracellular fluid volume (Fig. 6, upper right). Intracellular hydration tended to be increased at 3 hr in the glycine experiments, but this difference from baseline was not significant.

The increased extracellular impedance in the leg indicated a reduction of the fluid volume, while the intracellular impedance did not change significantly (Fig. 6, bottom).

TABLE I. Results of 24-hr Recordings of Electrocardiogram During Normal Activity (Control), Day of Glycine Infusion, and Day of Mannitol Infusion*

	Control	Glycine 1.5% + ethanol 1%	Mannitol 3% + ethanol 1%
Normal QRS (10^3, n)	4.2 (3.6–4.8)	4.1 (3.4–5.0)	4.1 (3.4–4.9)
Aberrant QRS (n)	3.2 (0.4–62.6)	0.6 (0.3–36.4)	0.6 (0.3–46.3)
Missing QRS (n)	3.5 (0.8–9.1)	2.3 (0.5–13.1)	3.0 (0.9–7.7)
Irregular rhythm (%)	7.6 (0.8–14.2)	8.0 (0.5–27.5)	6.3 (0.5–23.1)
SVES (n)	2.9 (0.7–8.1)	3.2 (0.5–9.0)	2.1 (0.2–9.3)
VES (n)	1.0 (0.2–6.8)	0.3 (0.1–9.0)	0.4 (0.1–16.0)
ES (n)	10.7 (2.5–81.7)	8.5 (2.9–33.7)	4.9 (1.8–19.1)

*Data represent the mean for 1 hr and are given as the median and the 10th and 90th percentiles. SVES, supraventricular extrasystolic beats; VES, ventricular extrasystolic beats; ES, extrasystolic beats.

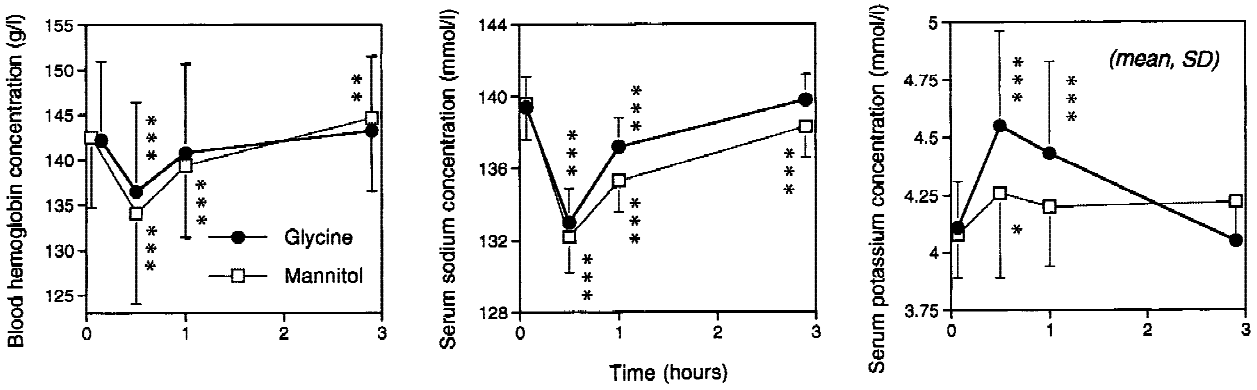

Fig. 2. The blood hemoglobin (**left**), serum sodium (**middle**), and serum potassium (**right**) concentrations during and after intravenous infusion of 15 ml/kg of glycine 1.5% and mannitol 3%, both with ethanol 1% added, over 30 min in 12 volunteers. A significant change from baseline level is indicated by $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$.

DISCUSSION

This study outlines certain differences between glycine and mannitol solutions, which are alternative irrigating fluids for TURP, when approximately 1.25 l of each are given intravenously to relatively young male volunteers. Absorption of this volume of glycine 1.5% during TURP is associated with a statistically increased risk of symptoms, such as nausea and arterial hypotension [15]. In the present study, glycine was followed by more symptoms than mannitol, although most of them were very mild. A similar difference was recently found in a clinical study of 52 patients who had absorbed glycine or mannitol solution during TURP [2].

The infused volume was apparently too small to impair cognitive function as detectable by the mental status test. Confusion is a frequent complication of TURP and is usually attributed to old age, cardiovascular disease, and chronic medication, but glycine absorption is also a contributing factor [15,16]. The plasma ammonia level may increase after glycine but not after mannitol administration [17] and, therefore, hyperammonemia is one mechanism that explains some cases of mental alterations after glycine absorption [18,19]. In the present study, however, the rise in the blood ammonia level up to 30 min after ending the infusion, when it is expected to peak [20], was fairly small. Alcohol is another toxic agent that might impair cognitive function. In Scandinavia and the United Kingdom, the occurrence and amount of fluid absorption are often determined with the aid of ethanol monitoring. This method exposes patients who absorb irrigating fluid to a certain alcohol load, but the ethanol levels reached are not high enough to cause alcohol intoxication when the fluid contains only 1% of ethanol [5]. In our volunteers, much of the ethanol was likely to have been metabolized when the second mental status test was performed [17,19].

The distribution of the infused fluid might also be associated with adverse effects. Cerebral edema has

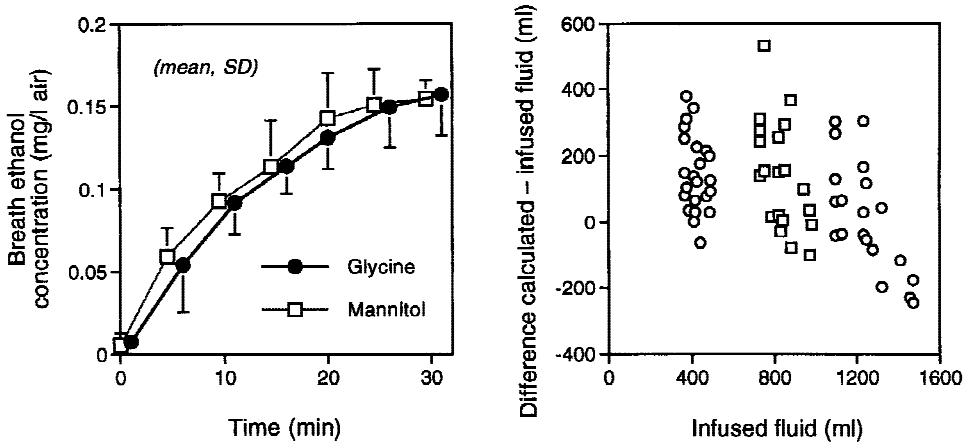

Fig. 3. Left: Ethanol concentration in the end-expiratory air during intravenous infusion of irrigating fluid containing 1% of ethanol. **Right:** The difference between the absorbed volume as indicated by a nomogram (shown in Fig. 4) and the infused amount vs. the infused amount in each volunteer at 10 min (circles at ≈400 ml), 20 min (squares at ≈800 ml), and 30 min of the infusion (circles at ≈1,200 ml).

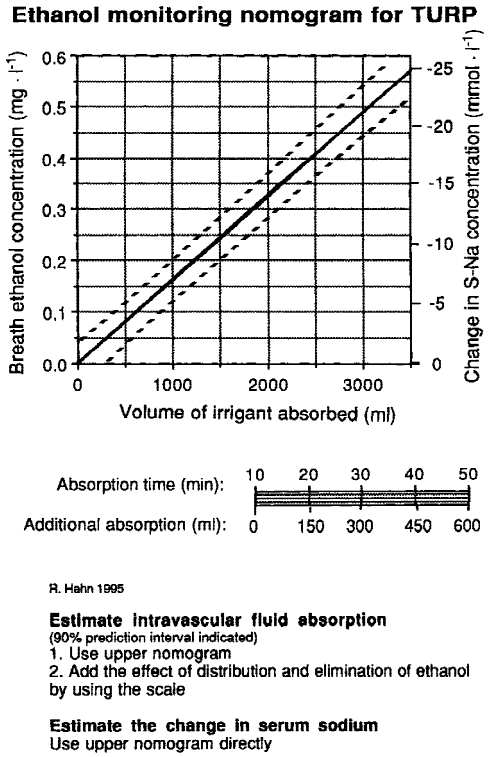

Fig. 4. Nomogram for estimation of the amount of absorbed irrigating fluid containing 1% of ethanol and the decrease in the serum sodium level by measuring the ethanol concentration in the expired breath. From Hahn [5], used with permission.

been implicated as a major source of symptoms when irrigating fluid is absorbed [21,22]. Istre et al. [8] reported signs of cerebral edema associated with nausea after absorption of as little as 1,000 ml of glycine 1.5% in women undergoing endometrial resection. We could not replicate this finding, however, as 1,250 ml of irrigating fluid did not result in cerebral edema detectable by computerized tomography. The glycine level is low in the cerebrospinal fluid of males [23], and the sodium changes are small [24] despite marked hyperglycinemia and hyponatremia, and this might explain why cerebral edema did not develop in our volunteers. Although cerebral edema probably develops in response to larger amounts of glycine 1.5%, several studies showed that other mechanisms than hyponatremia and hypoosmolality may account for an unfavorable course [3,4,25]. In mice, glycine mixed in normal saline is as dangerous as glycine in sterile water [25] and, in both mice and rabbits, glycine is associated with a poorer chance of survival than is mannitol, although mannitol induces a more pronounced hyponatremia [3,4].

The mathematical method used to calculate the average distribution of fluid between cells and noncells in the whole body confirms that glycine, but not mannitol, increases the fluid content of cells [1]. This accumulation of fluid is probably long-lasting, as it was still present 3 hr after starting the infusion. In contrast, the intravascular and interstitial fluid volumes underwent two phases. After a transient increase, these volumes were reduced and remained below baseline at 3 hr.

The acute hyponatremia induced by infusion of the irrigating fluid, which averaged 7 mmol/l, is due both to dilution and to urinary losses of sodium [1]. The volunteers excreted more water than the infused volume and, naturally, more electrolytes, as the irrigating fluids contained no electrolytes. The combined effects of volume and salt losses in excess to what was infused is sufficient to explain the coexistence of hypovolemia and a normal or slightly lowered serum sodium level at the end of the study.

The depletion of extracellular fluid was confirmed

TABLE II. Urinary Excretion of Fluid and Electrolytes After Intravenous Infusion of 15 ml/kg of Two Irrigating Fluids Over 30 Min*

Variable	Time interval	Glycine 1.5% + ethanol 1%	Mannitol 3% + ethanol 1%	Wilcoxon's matched-pair test
Urine volume (ml)	0–1 hr	513 (248–880)	788 (520–1,248)	$P < 0.02$
	0–3 hr	1,238 (935–1,838)	1,813 (1,100–2,165)	$P < 0.03$
Na excretion (mmol)	0–1 hr	30 (6–52)	31 (16–52)	
	0–3 hr	61 (13–90)	68 (36–113)	$P < 0.04$
K excretion (mmol)	0–1 hr	13 (4–23)	12 (4–20)	
	0–3 hr	24 (11–48)	24 (12–34)	

*Data are the median and the 10th and 90th percentiles.

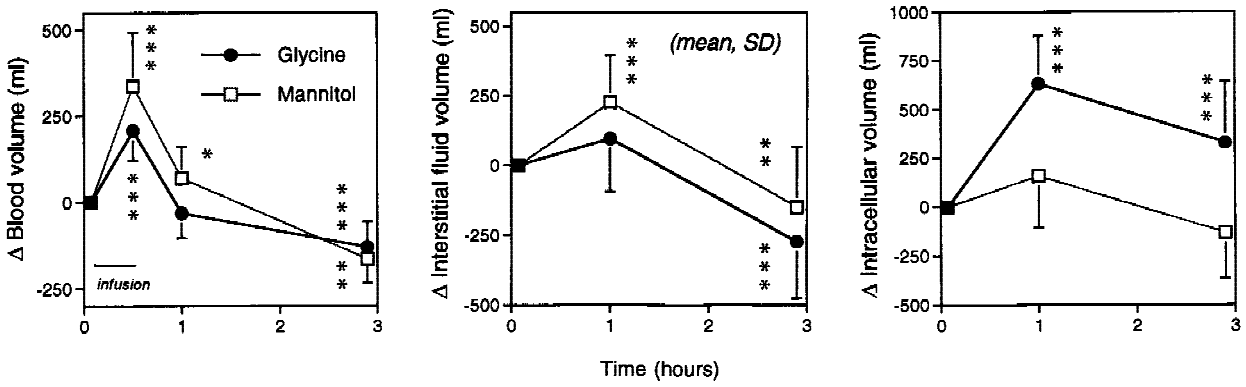

Fig. 5. Changes in the blood (**left**), interstitial fluid (**middle**), and intracellular fluid (**right**) volumes after intravenous infusion of irrigating fluids in 12 male volunteers as calculated from the volume of distribution of serum sodium. A significant change from baseline level is indicated by $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$.

by the whole-body bioimpedance recordings. They also supported the effects of irrigating fluid on the intracellular fluid volume shown by the mathematical method. The difference between the two methods was limited to the transient increase of the extracellular fluid volume after the infusion, which was not indicated by the bioimpedance. The changes obtained with these methods would be more similar, however, if we had considered the increase in body weight induced by the infused fluid when making the second bioimpedance recording.

Our view that glycine and, to a lesser degree, mannitol enter the cells and bring along water, is further evidenced by the data on serum potassium. Swollen cells decrease their volume by pumping out potassium [26], and glycine induces hyperkalemia [19] by reducing the amount of intracellular potassium [3]. The hyperkalemic effect of a glycine solution is related directly to its concentration [27]. In the present study, glycine increased the serum potassium level much more than the mannitol infusions did. This difference was not caused by hemolysis, as the lactate dehydrogenase concentration becomes diluted rather than increased when glycine 1.0%, glycine 1.5%, and mannitol 3% with ethanol 1% are given by intravenous infusion [17]. A glycine solution does not cause hemolysis until its concentration is below 1.0%, and the presence of ethanol slightly reduces this tendency [28].

Segmental measurements using the bioimpedance technique are less well-evaluated than whole-body measurements, but the measured impedance is still largely dependent on the intra- and extracellular water distribution, the impedance being inversely proportional to the water content. At low radio frequencies, the current passes mainly through the extracellular fluid, while the flow of current at higher radio frequencies can penetrate the cell membranes, and the impedance then reflects the total body water volume [12,13]. Therefore, the recorded increase in extracellular impedance in the leg indicates that fluid was removed from the tissue. Extracellular dehydration was present in the legs of our volunteers at the end of the study, while the changes in intracellular fluid content did not reach statistical significance. These results are consistent with a distribution of fluid corresponding to a regional uptake of glycine. After a glycine load, the concentration of this amino acid is higher in the

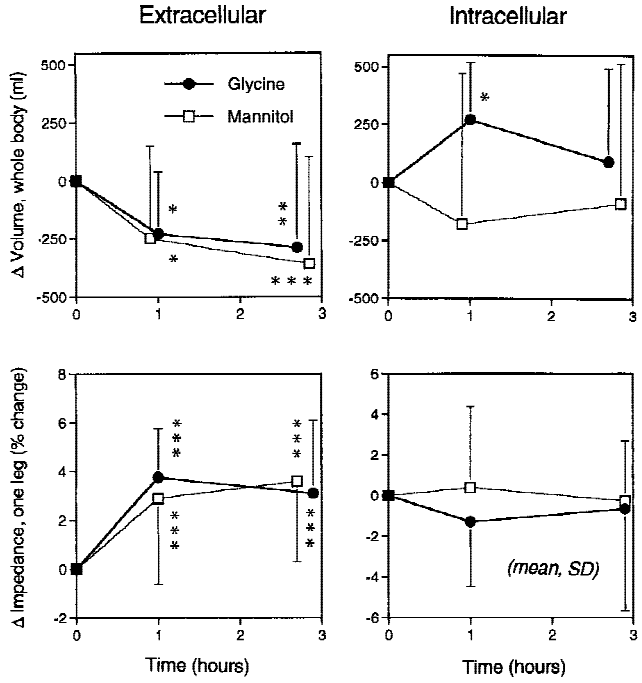

Fig. 6. Changes in the extracellular (**left**) and intracellular (**right**) fluid volumes in the whole body (**top**) and in one leg (**bottom**), as indicated by bioimpedance after intravenous infusion of two irrigating fluids in 12 volunteers. A significant change from baseline level is indicated by $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$.

liver, kidney, and myocardial tissue than in skeletal muscle [29], and is very low in the brain [30]. In the rabbit, cellular swelling in the heart, liver, and kidneys (but not the brain) developed when glycine solution was infused, while no edema was observed after mannitol [3]. The half-life of glycine in vitreous fluid [23] and in skeletal muscle cells [31] is much longer than in plasma and, therefore, glycine can probably cause local edema by virtue of osmosis.

Hemodynamic changes associated with glycine absorption during TURP usually consist of a decrease in arterial pressure, which is sometimes preceded by a transient rise [15,21,22,28]. Hypotension occurs equally often after TURP associated with mannitol absorption as with glycine [2]. The present study confirms that glycine, but not mannitol, increases the arterial pressure; the glycine infusions were also followed by a late but minor reduction of pressure. Hypotension, which is the clinically important event, has been explained by extracellular dehydration and hypovolemia during TURP [32], and this view is consistent with the present calculations of fluid distribution. Disturbances of heart function [33–35] and T-wave alterations [36] have also been reported after glycine absorption during TURP, but no such adverse effects were detected by the electrocardiograms in our volunteers. Thus, the two main investigative parts of this study, consisting of computerized tomography and 24-hr recordings of the electrocardiograms for evaluating disturbances of cardiac function, were essentially negative.

As both irrigating fluids contained a small amount of ethanol, the absorbed volume could be estimated from the amount of ethanol measured in the patient's exhaled breath. The measured breath alcohol concentrations were the same as those found in previous reports [17,19], but the present results were expressed in a new unit, mg/ml of air. The principle of the "breathalyzer" is that ethanol concentrations in the exhaled gas reflect the concentrations in the blood, and 0.23 g/l in the blood (23 mg/100 ml) corresponds to about 0.1 mg/l in expired air.

The results of the breath test were applied to the nomogram shown in Figure 4, which is the one approved for clinical use in the European Union [5]. The nomogram, however, usually gave too high a figure for absorption during the first 20 min of our infusions. The "overshoot" of the ethanol level was probably due to the fact that the breath tests were done during an ongoing infusion of fluid. In the clinic, breath samples are taken during temporary stops in the operation, because the patient sometimes moves when taking a deep breath. Under such conditions, the breath ethanol level falls slightly due to a distribution effect [37]. This view is consistent with the smaller "overshoot" with the passage of time, as a larger fraction of the infused alcohol has then been distributed in the total body water [38].

The present study was designed to mimic fluid absorption when it occurs by the direct intravenous route. Irrigating fluid can also be deposited in the retroperitoneal space following instrumental perforations of the prostatic capsule. In these situations, electrolytes travel into pools of fluid, thus creating late hyponatremia and a reduction of blood volume [39,40]. Bradycardia, arterial hypotension, and failed spontaneous diuresis occur between 2–3 times more often when glycine solution is deposited in the retroperitoneal space compared to when it is absorbed by the direct intravenous route [14]. Although this form of absorption was common in the 1950s and 1960s [41,42], studies published in recent years show that fluid absorption predominantly occurs by the intravenous route [2,5,15,28,36,43,44], probably because better surgical instruments and light sources make it easier for the surgeon to avoid the prostatic capsule.

In conclusion, the influence on arterial pressure and the higher incidence of symptoms associated with glycine 1.5% found in the present study, together with previous clinical and experimental evidence [2,3,4,18], lead us to believe that mannitol 3% is the better irrigating solution during genitourinary surgery. The

fluid and electrolyte losses associated with infusion of both urological irrigating fluids promote a hypovolemic state.

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APPENDIX

Diffusion of Water to the Cells

The distribution of infused water between body fluid compartments was calculated by assuming that the extracellular fluid volume (ECF_o) makes up 20% of the body weight and corresponds to the volume of distribution of sodium. The change in water content of the intracellular fluid compartment (ΔICF) after infusion of a volume of irrigating fluid (IFV) was calculated as the difference between the change in sodium space and the expected change in water content of the ECF. The first variable was accepted as the true ECF volume and was obtained as the estimated amount of sodium in the ECF (Na_{ECF}) divided by the serum sodium concentration at any time ($S\text{-}Na_n$). The Na_{ECF} was calculated from the equation:

$$Na_{ECF} = ECF_o \times S\text{-}Na_o - U\text{-}Na_{loss}$$

where $S\text{-}Na_o$ is the plasma sodium concentration before the experiment and $U\text{-}Na_{loss}$ is the quantity of sodium ions lost in the urine.

The *expected ECF volume* was obtained from the following equation:

$$ECF_n = 0.2 \times \text{body weight} + \text{IFV} - \sum \text{urine volume}$$

where the last term denotes the cumulative volume of urine excreted during the experiment. Then, the ΔICF could be obtained as:

$$\Delta ICF = ECF_n - (Na_{ECF}/S\text{-}Na_n).$$