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Dose-dependent half-life of glycine

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Summary. The serum concentration of glycine was measured at hourly intervals after administration of between 10 and 91 g glycine to 17 patients undergoing transurethral resection of the prostate and of between 15 and 22 g glycine to 18 volunteers by intravenous infusion. The apparent half-life of glycine varied 10-fold (range 26–245 min) and increased in direct proportion to the amount of glycine given. This result can be explained by assuming a marked intracellular accumulation of a surplus of glycine. The dose-dependent half-life means that patients who absorb large amounts of irrigating fluid are exposed to excessive blood levels of glycine for a prolonged period of time.

Key words: Blood – Glycine – Pharmacokinetics

During transurethral operations on the prostate, patients may absorb some of the solution used to irrigate the bladder. The most widely used irrigant is 1.5% glycine in water. Therefore, hyperglycinaemia is common during these operations, even to the extent that toxicity symptoms ensue [1, 2, 4]. However, studies of glycine absorption during transurethral operations give different values for the rate of elimination of a surplus of this amino acid. The half-life of glycine has been found to be 63 min [6], 85 min [11], 100 min [7] and 6 h [12]. The half-life seems to be longer after transurethral operations in which toxic amounts of irrigant are absorbed [1, 10]. These reports suggest that the ability to eliminate glycine is reduced in some patients, which results in prolonged exposure to potentially toxic blood glycine levels during the postoperative follow-up.

The aim of this study was to try to find an explanation for the variable elimination rate by examining the half-life of glycine after administration of a wide range of toxic and non-toxic doses under surgical and experimental conditions.

Materials and methods

Data were collected from two series of patients. Both study protocols were approved by the local ethics committee. The first series of patients consisted of 17 men (median age 68 years, 58–83 years) who had undergone transurethral resection of the prostate. In all cases, absorption of irrigating fluid into the circulation had been detected by an acute decrease in the serum sodium concentration during the operation. The amount of glycine absorbed was calculated from volumetric measurements of the irrigating fluid balance. In most cases this was done at the end of each 10-min period during the operation using a "regular-interval monitoring" programme [4]. The glycine concentration in venous serum was measured at 0, 30, 60 and 120 min or at 180 and 360 min after the prostatic resections.

In the second series, 18 male patients aged between 26 and 79 years (median 68 years) gave their informed consent to be given an intravenous infusion of 1000 ml of either a 1.5% or a 2.2% solution of glycine over a period of 20 min. The glycine concentration in venous serum was measured at the end of the infusion and 30, 60 and 120 min later.

The analyses of amino acid concentrations were performed with a Liquimat III (Kontron, Zurich, Switzerland). The serum sodium and serum potassium concentrations were measured by flame photometry. Serum osmolality was determined by freezing-point depression. The distribution volume for glycine was obtained as the dose divided by the serum concentration at the end of amino acid administration. The half-life of glycine was calculated by linear regression analysis of the logarithm of serum concentration *versus* time [9]. Simple and multiple linear regression analysis and the paired *t*-test were employed for statistical analysis.

Results

At the end of amino acid administration, the distribution volume for glycine was 35 ± 15 l (mean ± SD); this increased with the administered glycine dose ($r = 0.52$; $P < 0.004$), amounting to 20 l for the smallest doses and to about 60 l for the largest. Despite this considerable size, glycine had not always achieved its final distribution volume. Therefore, the serum samples obtained at this time were not included in the calculation of the half-life.

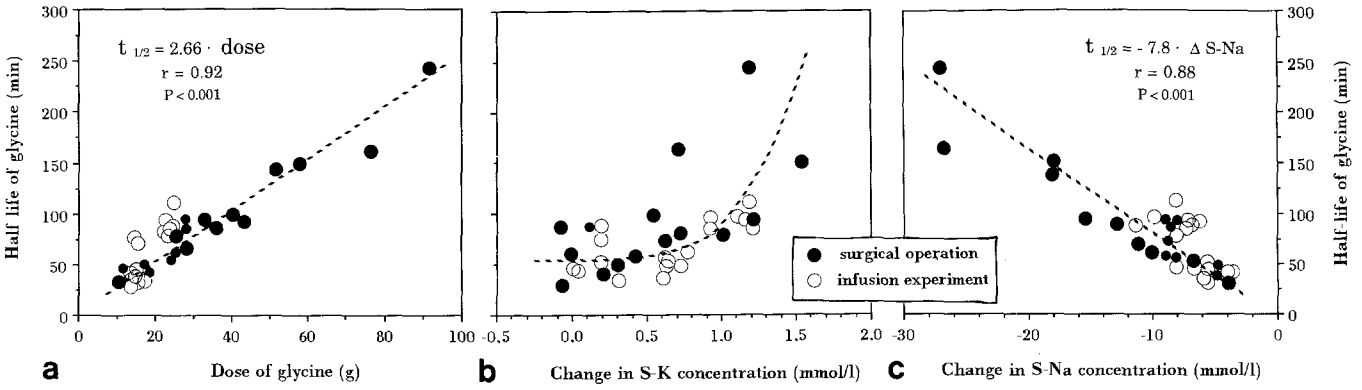

Fig. 1. Administered dose of glycine (a), change in serum potassium (*S-K*) concentration (b) and change in serum sodium (*S-Na*) concentration (c) *versus* the elimination rate (half-life) in 35 men receiving urological irrigating fluid containing 1.5% or 2.2% glycine

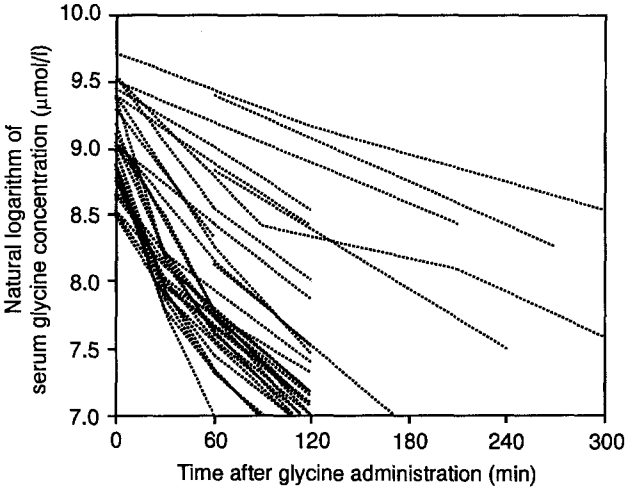

Fig. 2. Serum glycine concentrations after administration of glycine (note log scale). Parallel slopes indicate identical half-lives

The serum glycine concentration 30–60 min later ranged from 2278 to 13350 μmol/l, and all further post-operative decrease in serum glycine followed the rule of constant proportion. Hence, the half-life of glycine was calculated using the logarithm of serum concentration from 30–60 min and onwards [9].

The result of this analysis showed that the half-life of glycine varied greatly, and ranged between 26 and 245 min (median 75 min). The half-life was longer when a larger amount was administered (Fig. 1a) and when the serum concentration was higher (Fig. 2). There was also a strong linear correlation between the half-life of glycine and the level of irrigating fluid administration, as reflected by a decrease in serum sodium during the experiment or the operation (Fig. 1c).

Several health status factors and the operation data were collected, but the dose of glycine was the only predictor that correlated with the half-life of glycine (multiple regression analysis). Factors having no bearing on the half-life included body weight (median 74 kg, range 60–98 kg) and the serum creatinine concentration (median 94 μmol/l, range 51–245 μmol/l).

During glycine administration there was an increase in serum potassium concentration from 4.0 ± 0.4 mmol/l to 4.6 ± 0.4 mmol/l (mean ± SD; $P < 0.001$; Fig. 1b) and a decrease in serum osmolality from 294 ± 6 to 291 ± 6 mosmol/kg ($P < 0.005$).

Discussion

A surplus of glycine is distributed over a large volume in the body [1] and the present calculations of apparent half-life were based on serum samples collected 30–60 min after glycine administration and onwards in order to allow complete equilibration of the amino acid in the body fluids. The data points were too few in number to allow compartmental analysis, but there was good logarithmic linearity with the model used. The amount of glycine administered corresponds to about 40 to 400 times the physiological amount in a healthy adult and represents a fairly extreme situation with regard to the exchange of the amino acid between distribution compartments and its metabolism. However, very high serum glycine levels frequently occur in transurethral resections in which glycine is used for bladder irrigation.

The results demonstrate a 10-fold variation in the apparent half-life of glycine, with an increase in direct proportion to the glycine load. The dose-dependent apparent half-life signifies that patients who absorb very large volumes of irrigating fluid are exposed to excessive serum glycine levels during a longer period of time than expected based on a conventional pharmacokinetic approach, which holds that the elimination half-life remains unchanged when the dose is increased [9].

The present results can be explained by assuming a marked intracellular accumulation of a surplus of glycine. Skeletal muscle in particular is a quantitatively important reservoir for this amino acid. In a recent study the glycine concentrations in plasma and muscle were already equal within 1 h after its administration, while 3 h later the high concentration persisted in muscle but had decreased in plasma [7]. The change in plasma concentration during

this period of observation was probably due to a combination of metabolism and redistribution. Glycine is metabolized in the liver, and therefore its diffusion from the intracellular compartment back into the circulation will prolong the apparent elimination rate.

Evidence of a pronounced intracellular distribution of glycine is also obtained by comparing the distribution volumes of glycine and irrigant water. The latter, which can be estimated from the dilution of the serum sodium level, is slightly larger than the extracellular fluid volume at the end of surgery [2]. Each change in serum sodium caused by absorption of irrigating fluid should ideally be accompanied by 1.4 times the increase (with 1.5% glycine solution) or twice the increase (with 2.2% glycine solution) in the serum glycine level. In the present study the serum glycine level at the end of surgery was only about 70% that which would be expected from these considerations – a finding which has been confirmed by other reports [1, 10, 11, 14]. The difference in distribution volume between glycine and the irrigant water is maintained by shift of potassium (Fig. 1b), by an increase in the serum concentrations of all non-essential amino acids other than glycine [1] and possibly by other unknown mechanisms.

The variable elimination rate of glycine is not surprising from a pharmacokinetic point of view. For most compartmental models the dose divided by the area under the entire concentration-time curve is always the same, which gives rise to the concept of a constant whole-body clearance [9]. Increasing intracellular disposition resulted in lower serum glycine levels than might be expected during the operation, which had to be accompanied by higher serum concentrations than expected during the postoperative follow-up in order to maintain a constant whole-body clearance. The elevation of the serum glycine levels due to redistribution were sufficient to prolong markedly the time required for the glycine levels to return to normal.

The reported differences regarding the half-life of glycine cannot be explained by variations in kidney function. The renal excretion of 15–40 g glycine amounts to only between 5% and 10% of the administered dose [3, 5]. This fraction increases for higher doses [13] but this would, if anything, shorten of the half-life.

The hypothesis of a correlation between lowered intraoperative serum glycine levels and a dose-dependent terminal half-life is supported by experiments performed on sheep. Serum glycine levels increase nearly as expected from the dilution of serum sodium, which suggests a limited intracellular accumulation of glycine. As would be expected from the present study, the elimination rate of glycine in this animal does not seem to be dose-dependent. The half-life was about 120 min when either 33 g [4] or 85 g glycine were administered [13]. No increase in the serum potassium level occurs, which supports the hypothesis that hyperkalaemia is related to intracellular uptake of glycine.

The pharmacodynamic implications of the dose-dependent half-life of glycine are not clear. Large amounts of glycine give rise to symptoms involving the central nervous system, and serum glycine levels in excess of 10000 μmol/l are usually associated with toxic symptoms and elevated blood ammonia levels [1, 10, 14]. Consequently, many patients in the present study experienced symptoms of malaise, nausea and vomiting [2, 6, 7]. However, it is not known whether toxic symptoms are related to the dose or to the serum level of glycine. By virtue of its redistribution from muscle cells, a patient becomes subjected to prolonged exposure to high serum levels of glycine, which may explain some cases of long-lasting hyperammonaemic encephalopathy after transurethral operations [2, 8, 12]. On the other hand, the lowering of serum glycine levels during surgery clearly attenuates the most severe hyperglycinaemic episodes.

In conclusion, intracellular accumulation of glycine is prominent when toxic amounts of this amino acid are given. This results in lower than expected serum levels of glycine during its administration and a dose-dependent elimination rate.

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