# Resin hemoperfusion in dogs intoxicated with ethchlorvynol (Placidyl®)

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**Resin hemoperfusion in dogs intoxicated with ethchlorvynol (Placidyl®).** Kinetic parameters were studied to determine the effectiveness of hemoperfusion in removing ethchlorvynol from the plasma and red blood cells (RBC) of intoxicated dogs. Perfusion columns contained polystyrene/divinyl benzene resin (XAD-4 Amberlite®). Column clearances of ethchlorvynol averaged $96.5 \pm 0.4\%$ of the plasma flow rate (mean $\pm$ SEM, 9 dogs). Plasma ethchlorvynol $t^{1/2}$'s during preperfusion periods averaged 94.1 hr. During hemoperfusion, $t^{1/2}$'s averaged 3.8 hr, or 90.3 hr shorter than at the endogenous rate of detoxication. There was no significant difference between preperfusion and postperfusion half lives. An estimate based on plasma column clearance suggests that $1.5 \pm 0.1$ g ethchlorvynol, or $19.0 \pm 2.8\%$ of the dose, was removed by hemoperfusion. The amount eluted from the resin was $2.9 \pm 0.3$ g ($37.2 \pm 5.8\%$ of the dose), or about twice the amount apparent from plasma clearance alone. Further, the volume of distribution of ethchlorvynol was $2.3 \pm 0.2$ liters/kg, suggesting significant distribution to intracellular and extravascular compartments. The results show that resin hemoperfusion removes a large fraction of ethchlorvynol from intoxicated dogs, and greatly adds to endogenous mechanisms for elimination. Ethchlorvynol was removed from RBC directly, and ultimately from extravascular sites as well.

**Hémoperfusion sur résine chez des chiens intoxiqués par l'éthchlorvynol (Placidyl®).** Afin de déterminer l'efficacité de l'hémoperfusion dans la soustraction d'éthchlorvynol du plasma et des hématies de chiens intoxiqués, les paramètres cinétiques ont été mesurés. Les colonnes de perfusion contenaient une résine polystyrène/divinyl benzène (XAD-4 Amberlite®). La clearance de l'éthchlorvynol par les colonnes était en moyenne de $96,5 \pm 0,4\%$ du débit plasmatique (moyenne $\pm$ SEM, 9 chiens). La plasmatique de l'éthchlorvynol $t^{1/2}$'s pendant la période préalable à la perfusion était de 94, 1 heures. Pendant l'hémoperfusion, $t^{1/2}$'s était en moyenne de 3,8 heures, soit 90,3 heures de moins qu'au cours de la détoxication spontanée. Il n'a pas été observé de différence entre les demi vies avant et après perfusion. Une estimation fondée sur la clearance des colonnes suggère que $1,5 \pm 0,1$ g d'éthchlorvynol, soit $19,0 \pm 2,8\%$ de la dose a été soustrait par l'hémoperfusion. La quantité éluée de la résine a été de $2,9 \pm 0,3$ g ($37,2 \pm 5,8\%$ de la dose), soit le double de la quantité évaluée à partir de la clearance du plasma. De plus, le volume de distribution de l'éthchlorvynol était de $2,3 \pm 0,2$ litres/kg, ce qui suggère une distribution importante dans les compartiments intracellulaire et extravasculaire. Les résultats montrent que l'hémoperfusion sur résine soustrait une fraction importante de l'éthchlorvynol chez des chiens intoxiqués et ajoute une élimination importante aux mécanismes endogènes. L'éthchlorvynol a été soustrait des hématies directement et finalement des sites extravasculaires aussi.

It is known that risks of morbidity and mortality from poisoning increase with the length of recovery, particularly when stage-IV coma is involved [1–3]. Some central-nervous-system depressants, including ethchlorvynol, have elimination half-lives ($t^{1/2}$) that exceed 100 hr [4]. Recovery from stage-IV coma could take many days because 3.3 half-lives are needed to remove 90% of the drug, assuming a constant rate of elimination. The use of hemoperfusion is justified if it can significantly add to endogenous elimination [1, 5, 6] and thereby shorten the recovery time.

Three types of adsorbents have been used in perfusion devices for drug removal: activated charcoal, ion-exchange resins, and aromatic resins [7]. The aromatic resins, XAD-2 Amberlite® and XAD-4 Amberlite® (Rohm and Haas Co., Philadelphia), have a special affinity for lipophilic drugs [8]. The XAD-4 resin is commercially available and has more than twice the surface area, greater porosity, but a smaller average pore size than the earlier version.

Aromatic resins have been studied in vivo in dogs and humans intoxicated with barbiturates [8–13], cephalothin and clindamycin [14], digoxin [15–17], ethchlorvynol [10], glutethimide [8–10, 13], methaqualone [11], methotrexate [18], theophylline [19], and tricyclic antidepressants [13]. In vitro perfusion with the XAD-4 resin has been tested for adsorption of procainamide, *N*-acetylprocainamide, and quinidine [20].

Aromatic resin hemoperfusion in ethchlorvynol intoxication has been reported only in a single human patient [10] and involved the earlier XAD-2

resin. As many as nine human patients [21, 22] and one dog [23] intoxicated with ethchlorvynol have been perfused with activated charcoal, but reports of XAD-4 perfusion in ethchlorvynol intoxication could not be found in the literature. Therefore, its ability to add to the endogenous elimination of this drug has not been established.

Hemoperfusion often has involved more than one removable drug, and its usefulness in single drug poisoning seems obscure. Effectiveness in multiple drug poisoning may be difficult to define without first characterizing its single drug capability. The present study tested XAD-4 perfusion in single drug intoxications, and effectiveness was assessed by comparing its drug removal rate to the rate of endogenous elimination.

## Methods

Mongrel male or female dogs (mean weight, 22.1 kg) were given 350 or 400 mg/kg liquid ethchlorvynol peroral. The animals were fasted for 48 hr and deprived of water for 24 hr to maximize drug absorption and minimize pulmonary complications. The viscous drug was administered through a polyethylene (PE-240) stomach tube which was then flushed with saline to assure quantitative delivery. The dogs became comatose, and surgery could be performed without supplemental anesthesia within 5 hr of dosing. Assessment of stage-IV coma was based primarily on the need for respiratory assistance [3]. The animals were intubated with a cuffed endotracheal tube, and vital signs were monitored periodically. During perfusion, animals that exhibited the righting reflex were supported upright in a sling and frame (Alice King Chatham Medical Arts, Los Angeles, California), thus preventing the need for supplemental anesthesia.

*Blood sampling.* Plasma ethchlorvynol concentration was followed before, during, and after hemoperfusion to compare elimination half-lives between these periods. This provided a rigorous assessment of effectiveness, with each animal as its own control. Blood was drawn initially from a brachial vein by percutaneous puncture until the animals could tolerate surgery and then from a catheterized jugular vein for all other preperfusion and postperfusion samples. A dextrose-in-saline solution was administered through an i.v. apparatus set to maintain patency and provide fluid replacement. The samples were drawn after temporarily removing slightly more than the tubing deadspace volume into another syringe while the i.v. drip was blocked. Syringes for preperfusion and postperfusion samples were heparinized with very small

volumes of concentrated heparin (10,000 U/ml) to avoid diluting the drug. A femoral artery and vein were catheterized for perfusion, and samples were drawn from each of the inflow and outflow lines of a pediatric arteriovenous blood-tubing set. Systemic heparinization (325 to 425 U/kg) during perfusion enabled the use of nonheparinized syringes. Duplicate hematocrits (Hct) were measured periodically from preperfusion and postperfusion samples and from all hemoperfusion samples.

*Hemoperfusion.* Custom-made columns (Extracorporeal Medical Specialties Inc., King of Prussia, Pennsylvania) contained about 430 g (wet weight) of copolymeric polystyrene and divinyl benzene resin (XAD-4 Amberlite®). The resin was primed by perfusing 4 to 5 liters of heparinized saline (10,000 U/liter) through the column, and was degassed by hammering the cylinder wall with a soft-headed mallet. Degassing and priming were considered satisfactory when bubbles no longer issued into the outflow line and the collected saline was clear and free of particulate. A dialysis roller pump was calibrated during priming by measuring 1-min samples at varied pump settings. Anaeroid manometers and fluid barriers (Extracorporeal) were attached to the inflow and outflow pressure monitor lines of the blood-tubing set to measure the pressure gradient across the column. The hemoperfusion circuit was tested for leaks by clamping the outflow line while saline was being perfused at about 200 ml/min through the system. Pressure in both lines was allowed to rise to 500 mm Hg before pump speed was reduced to zero. Rarely a column had to be replaced, and subtler leaks that caused a persistent loss of pressure were minimized by resecuring connections.

About half the volume of the priming solution (130 to 135 ml) was infused into the femoral vein at the start of perfusion to minimize the risk of shock. Blood flow rate was increased to 150 ml/min usually within 2 min and was maintained. Pressure about the column became stabilized within 5 min at 130 to 160 mm Hg in the inflow line and 70 to 90 mm Hg in the outflow line. An increase of 20 mm Hg or more in the inflow line only suggested coagulation in the column and was treated by injecting 1000 or 2000 U of heparin into the inflow line. Coagulation was avoided to assure continued blood flow over the maximum surface of resin and to simplify quantitative recovery of drug during elution.

*Resin elution.* At the end of perfusion, blood was returned to the animal by gravity feed. One of the ends of the cartridge was forcibly removed, and the resin was transferred to an empty oversized car-

tridge (Extracorporeal) because the resin expanded on addition of methanol. Cold saline (800 to 1000 ml) was poured onto the resin and collected as fraction I until the blood had come off and the original color of the resin was apparent. Then, several 300 to 500 ml fractions of methanol were added and collected at 4 to 5 ml/min. Because the resin absorbed methanol, the volume of each collected fraction was measured before being analyzed. Collection of fractions was continued until ethchlorvynol was essentially undetectable.

*Ethchlorvynol analysis.* Concentrations in plasma, RBC, urine, and methanol elution samples were determined routinely by the spectrophotometric method of Haux [24] with the following minor changes. Plasma was used for the blank in lieu of water, and 6 ml chloroform rather than 3 ml was used for the extraction to provide the minimum readable volume in a standard cuvette of a spectrophotometer (Spectronic-20). Four working standards containing 5, 10, 20, and 30 $\mu$g/ml in ethanol were determined with each analysis and comprised the linear range of the spectrophotometer. Unknown samples having concentrations in excess of 30 $\mu$g/ml were carefully diluted to within the linear range.

*Calculations.* Plasma column clearance of ethchlorvynol as a percent of plasma flow rate ($F_p$) was calculated by the equation $[(I-O)/I]100$, where I and O were plasma drug concentrations in the inflow and outflow lines, respectively. This expression can be interpreted without knowing whole blood flow rate ($F_b$), hematocrit, or $F_p$, and is similar to the extraction ratio used by others [7, 22].

The amount of drug removed from plasma based on column clearance ($A_p$) was calculated by an adaptation of the trapezoidal rule [25]:

$$A_p = T/2([(I - O)F_p]_0 + 2[(I - O)F_p]_1 + 2[(I - O)F_p]_2 + \ldots$$

$$\ldots 2[(I - O)F_p]_{n-1} + [(I - O)F_p]_n)$$

T was the time between samples, and $F_p$ was estimated from $F_b(1 - Hct)$ for each collection period. The subscripted numbers identify consecutive sample pairs having equal time intervals. The $I - O$ difference and $F_p$ were assumed to be constant between collections. This potential error was minimized by frequent sampling at short intervals. The total amount removed based directly on elution of the resin ($A_r$) was obtained by summing the products of concentration times volume from the collected fractions.

The drug elimination half-life ($t^{1/2}$), peak plasma drug concentration ($C_o$), and rate constant of elimination ($K_e$) were determined objectively for each of the preperfusion, hemoperfusion, and postperfusion periods by applying the least-squares statistical method to plasma drug concentrations and time (t), in hours, after dosing. A least-squares computer program converted drug concentration to the natural logarithm, base e (ln). Therefore, when drug concentration versus time was plotted on semilogarithmic coordinates, $K_e$ was directly equivalent to the slope of a best-fit line that described the rate of elimination. $K_e$ was calculated by the equation $\ln(C_b/C_a)/T$, where $C_a$ and $C_b$ were plasma drug concentrations at any two points a,b on the line, and T was the time $t_b - t_a$ between these points. The half-life is determined by $K_e$ and was given by the standard equation $- 0.693/K_e$, where $- 0.693$ is $\ln(^1/_2)$. Mean half-lives were determined by first taking the mean of the $K_e$'s from each period and then solving the equation.

The best-fit line was given by the equation $[\ln(C_t) = \ln(C_o) + K_e t]$ where $C_t$ is a statistical drug concentration corresponding to any chosen t based on the least-squares averaging of observed concentrations. When $t = 0$, the peak plasma concentration ($C_o$) is obtained and is the zero time intercept of the preperfusion line. $C_o$ was used to estimate volume of distribution ($V_d$) by the equation $X_o/C_o$, where $X_o$ was the dosage in milligrams per kilogram of body weight and $C_o$ was expressed in milligrams per liter. To be valid, all of the drug must be absorbed or $V_d$ would tend to be overestimated. Thus, an alternative approach was used that is relatively independent of drug absorption and makes use of a theoretically similar relationship between the net decrease in concentration due to hemoperfusion ($\Delta C_h$) and the amount of drug eluted from the resin ($A_r$). This $V_d$ was given by the equation $A_r/\Delta C_h$, where $A_r$ was expressed in milligrams per kilogram of body weight and $\Delta C_h$ in milligrams per liter. $\Delta C_h$ was estimated by taking the difference $[B - A]$, where B and A were the $C_t$'s obtained when the equations of the preperfusion and postperfusion lines, respectively, were solved for the moment hemoperfusion ended (usually $C_{34}$). Endogenous elimination during perfusion was excluded, and a postperfusion rebound in concentration was included in interpolating B and A.

Observed plasma drug concentrations that were significantly changing due to drug absorption or to distribution and redistribution phenomena were excluded from the derived pharmacokinetic parameters by evaluating the error of prediction in the least-squares program. This was to assure that the data
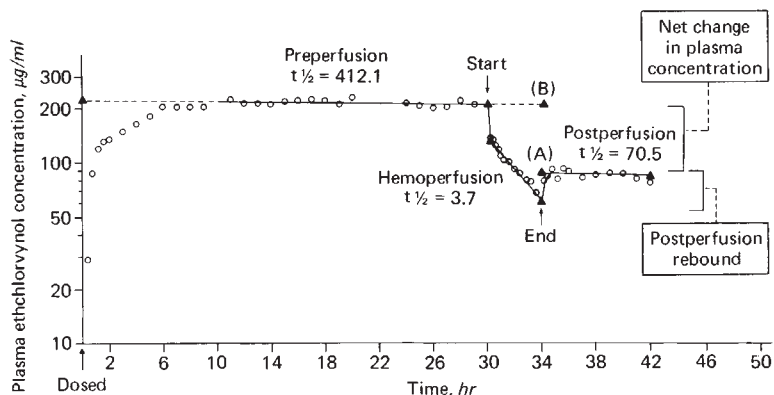
**Fig. 1.** *Concentration-time course of a typical hemoperfusion experiment. Circles* denote the observed plasma ethchlorvynol concentrations; *filled triangles*, the statistical concentrations from a least-squares analysis; *(B) and (A)*, the statistical concentrations at the instant hemoperfusion ended based on the preperfusion and postperfusion lines, respectively. The best-fit lines were drawn between the pairs of filled triangles at times 0 and 30 hr (preperfusion), 30.2 and 34 hr (hemoperfusion), and 34 and 42 hr (postperfusion).

represent the constant elimination phase of each of the preperfusion, hemoperfusion, and postperfusion periods. In a few cases, statistically excluded concentrations were included if they caused no significant change in $C_o$, $K_e$, or half-life, and concentrations in all samples taken from the inflow line during perfusion were always included.

The elimination of ethchlorvynol seemed to obey apparent first-order kinetics because the milligram quantity eliminated with time decayed with the plasma concentration but in a proportionally constant manner. Even though dosage, the length of the preperfusion and hemoperfusion periods, the size of the columns, and the $F_b$ were not varied, the drug concentrations at the start of perfusion and $\Delta C_h$ ranged widely and seemed to have a poor relationship to the effect produced in terms of the hemoperfusion $K_e$. This led to the derivation of a parameter that expresses the net change in drug concentration as a proportion of the beginning concentration. This parameter is given by the equation $[P^{1}/_2 = \ln(A/B)/ - 0.693]$, where $P^{1}/_2$ is the number of times the plasma concentration decreased by one half. Though arithmetically unitless, $P^{1}/_2$ was assigned units of half-lives. $P^{1}/_2$ is expected to increase with the length of perfusion if $F_b$ and the relative drug binding capacity or quantity of resin in the column do not change. However, $P^{1}/_2$ should be constant for a given time period and independent of the beginning plasma concentration if the rate of elimination is proportionally constant.

The statistical significance of difference in parameters between periods was determined by the dependent groups $t$-test. In the case of half-life, this test was applied to the $K_e$ differences between periods.

## Results

The observed plasma ethchlorvynol concentrations from a typical experiment are shown in Fig. 1 with the best-fit lines and related data. By comparison, the therapeutic range in the adult human has been reported to be 1 to 8 $\mu$g/ml [24]. This animal became comatose within 1.6 hr of dosing and required respiratory assistance by 4.0 hr (stage-IV coma). All perfused animals were in stage-IV coma at the beginning, awoke sometime during, and slept but would arouse when handled following the hemoperfusion period. One nonperfused dog remained comatose during a 5-day observation period.

The shallow slope of the preperfusion line yielded a biologic $t^{1}/_2$ of 412.1 hr (17.2 days). A half-life of such considerable length reflects that plasma concentration was changing very slowly and endogenous elimination was essentially negligible. The concentrations between 10 and 30 hr decreased by only 3.1 $\mu$g/ml and support this point. Half-lives during preperfusion and postperfusion periods of other experiments (Table 1) ranged widely, and a few were negative because the best-fit lines had slightly increasing slopes. In contrast, half-lives during perfusion were considerably shorter and made up a much narrower range. The mean difference between preperfusion and hemoperfusion $t^{1}/_2$'s was 90.3 hr (3.8 days) and is the additional time endogenous mechanisms would have taken to eliminate the amount of drug removed by 4 hr of perfusion. There was no significant difference between preperfusion and postperfusion half-lives.

The substantial decrease in concentration in the first 12 min of perfusion (Fig. 1) was observed in all other experiments and was excluded from deriva-

tion of the best-fit lines and half-lives because it did not seem representative of the constant and slower rate of elimination that followed. In one experiment, four samples were drawn from the inflow line at 3-min intervals initially, and it was found that the concentration decreased by 54.3 $\mu$g/ml (26.2%) within the first 3 min of perfusion. This decrease represented 42% of the net change in concentration produced by the total 4-hr perfusion period in this experiment. None of the priming solution was given

Table 1. Half-lives ($t^{1/2}$) of ethchlorvynol in intoxicated dogs treated with 4 hr of aromatic resin hemoperfusion[a]

| | $t^{1/2}$, hr | | |
|---|---|---|---|
| Exp. No. | Preperfusion | Hemoperfusion | Postperfusion |
| 1 | 57.0 (22) | 4.2 | 97.1 (8) |
| 2 | 59.6 (22) | 5.5 | 40.6 (10) |
| 3 | −882.4 (19) | 3.4 | 91.1 (6) |
| 4 | 79.9 (24) | 6.0 | −193.7 (9) |
| 5 | 29.9 (24) | 2.4 | 120.2 (9) |
| 6 | 445.7 (18) | 4.1 | 57.8 (10) |
| 7 | 412.1 (18) | 3.7 | 70.5 (11) |
| 8 | 114.6 (23) | 6.9 | 1281.9 (11) |
| 9 | 323.9 (13) | 2.5 | 372.9 (13) |
| Mean[b] | 94.1 | 3.8 | 107.1 |

[a] Number in parentheses equals number of plasma ethchlorvynol determinations contributing to the preperfusion and postperfusion half-lives. Each perfusion half-life was based on 13 inflow plasma ethchlorvynol determinations taken at 12- and 24-min intervals.

[b] This was obtained from the mean slope of each period. Mean difference between preperfusion and hemoperfusion half-lives is statistically significantly ($P < 0.0005$).

Table 2. Summary of ethchlorvynol column clearance and the amount of drug removed during hemoperfusion of several dogs intoxicated with ethchlorvynol

| | Ethchlorvynol column clearance[a] %$F_p$ | Ethchlorvynol removed[b] | | | |
|---|---|---|---|---|---|
| | | $A_p$ | $A_r$ | $A_p$ | $A_r$ |
| Exp. no | | mg | | % of dose | |
| 1 | 95.5 ± 2.7 | 961.7 | 1701.5 | 11.8 | 20.8 |
| 2 | 96.5 ± 2.1 | 901.0 | 1844.3 | 10.4 | 21.6 |
| 3 | 97.5 ± 2.3 | 1474.8 | 3139.1 | 15.2 | 32.2 |
| 4 | 97.6 ± 2.2 | 1223.6 | 2349.1 | 10.6 | 20.4 |
| 5 | 96.8 ± 3.5 | 1421.3 | 2753.9 | 26.2 | 50.8 |
| 6 | 97.0 ± 2.6 | 1815.8 | 4121.0 | 29.3 | 66.5 |
| 7 | 94.9 ± 3.3 | 1938.3 | 3728.3 | 25.8 | 49.6 |
| 8 | 98.1 ± 1.7 | 1517.1 | 2865.4 | 12.0 | 22.7 |
| 9 | 95.0 ± 4.4 | 1930.6 | 3238.4 | 29.8 | 50.0 |
| Mean | 96.5 | 1464.9 | 2860.1 | 19.0 | 37.2 |
| ± SEM | 0.4 | 129.0 | 269.0 | 2.8 | 5.8 |

[a] Clearance is expressed as a percent of plasma flow rate ($F_p$). Mean ± SD of each individual experiment was based on 13 pairs of inflow and outflow samples taken during perfusion.

[b] $A_p$ is the amount of drug removed from plasma alone; $A_r$, the amount of drug eluted from the resin. Mean difference between $A_p$ and $A_r$ of 18.2% is statistically significant ($P < 0.0005$)

to this animal, suggesting that the decrease was not a dilutional effect from administered fluid.

The statistical concentrations are also shown in Fig. 1. The difference between $C_{30}$ and $C_{34}$(B) shows that a very small decrease in concentration resulted from endogenous elimination during perfusion. The difference between $C_{34}$ based on the hemoperfusion line and $C_{34}$(A) indicates that a large cumulative postperfusion rebound occurred. Nevertheless, with both factors considered in the calculation, the net change in concentration ($\Delta C_h$ or [B − A]) demonstrates that a substantial effect resulted relative to that expected by endogenous elimination alone.

Table 2 lists data from several experiments summarizing the extraction of drug by hemoperfusion. Column clearances were extremely uniform. The total amount eluted from the resin ($A_r$) was about 2 times the amount removed from plasma ($A_p$) and implies that much more drug was extracted than can be accounted for in plasma alone. The size of $A_r$ indicates that a substantial percentage of the body drug burden was removed.

Extraction of drug from RBC's was tested directly in one experiment, and the data is plotted in Fig. 2 as a concentration-time curve of the ethchlorvynol differences between inflow and outflow samples of RBC's (solid line) and plasma (dashed line). The amount removed from RBC's was slightly but consistently greater than that from plasma. A RBC/plasma concentration ratio was found to be 1.12 ± 0.05 (mean ± SD, 13 inflow samples) and indicates that there was 12% more drug available in RBC's than in plasma. The RBC/plasma concentration ratio from 13 outflow samples was 2.73 ± 1.49, indicating that relatively more drug was left in RBC's than in plasma. This experiment corroborates the data in Table 2 and shows that a substantial amount of drug being extracted came from RBC's.

Apparent volumes of distribution ($V_d$) of ethchlorvynol using two methods of calculation are compared in Table 3, and the small difference in means reflects good agreement between these distinct approaches. $V_d$ approximates a hypothetical volume needed to accommodate both the drug amount ($X_o$ and $A_r$) and plasma concentration ($C_o$ and $\Delta C_h$) that are used in its calculation. Because whole blood volume in the dog has been estimated to be 0.08 liters/kg [26], $V_d$ of the sizable magnitude shown indicates major accumulation in one or more extravascular compartments. Because the product of blood volume times $\Delta C_h$ is only 3.5% of $A_r$ and therefore cannot account for the sizable amount removed, a $V_d$ based on these values implies that
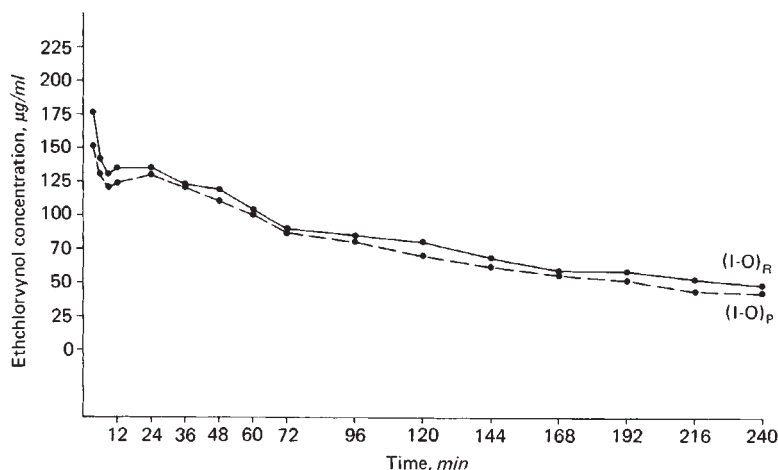
**Fig. 2.** *Comparison of the amount of drug removed from RBC's (R) and plasma (P) based on differences between drug concentrations in samples taken from the inflow (I) and outflow (O) lines during a single hemoperfusion experiment.*

most of the ethchlorvynol removed originated from the extravascular compartments.

Figure 3 graphically shows the data from a control experiment in which hemoperfusion was omitted and the animal allowed to detoxify itself through the first biologic half-life. The observed peak concentration at 11 hr was 150 $\mu$g/ml, and the first $t^{1}/_{2}$ concentration of 75 $\mu$g/ml was reached at 83 hr (3.5 days). This is an observed $t^{1}/_{2}$ of about 72 hr and lends credence to the statistically determined value shown above the best-fit line.

The effect of perfusion in terms of a proportional change in plasma concentration ($P^{1}/_{2}$) is shown in Table 4. Based on the mean preperfusion half-life (Table 1), 3.9 days would have been needed to de-

**Table 3.** Summary of volumes of distribution in ethchlorvynol-intoxicated dogs[a]

| Exp. no. | Wt kg | Volume of distribution | |
| --- | --- | --- | --- |
| | | $X_o/C_o$ | $A_r/\Delta C_h$ |
| | | *liters/kg* | |
| 1 | 25.5 | 2.51 | 2.11 |
| 2 | 24.8 | 2.56 | 2.21 |
| 3 | 24.3 | 2.84 | 2.01 |
| 4 | 28.8 | 3.21 | 3.33 |
| 5 | 13.8 | 1.31 | 2.47 |
| 6 | 15.5 | 2.24 | 2.78 |
| 7 | 18.8 | 1.79 | 1.63 |
| 8 | 31.5 | 2.97 | 2.48 |
| 9 | 16.2 | 1.80 | 1.56 |
| Mean | 22.1 | 2.36 | 2.29 |
| ± SEM | 1.9 | 0.21 | 0.19 |

[a] Two approaches to estimating $V_d$ are compared. $X_o$ is the dosage; $C_o$, the statistical peak plasma concentration; $A_r$, the amount eluted from the resin; $\Delta C_h$, the net change in plasma concentration during perfusion. The mean difference between $V_d$'s of 0.07 liters/kg (3.1%) is not statistically significant ($P = 0.4$).
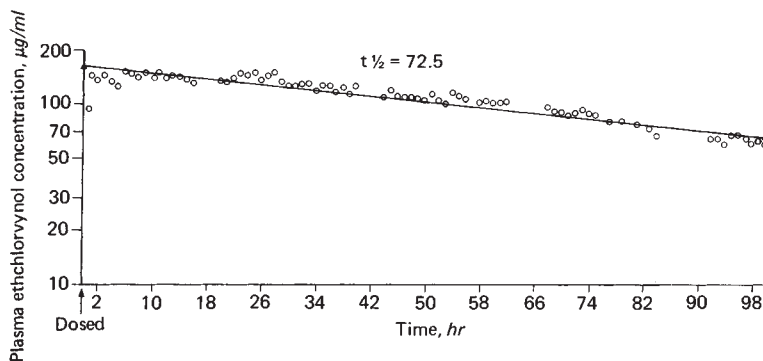
crease plasma concentration by one half-life if perfusion had not been performed. In contrast, the mean $P^{1}/_{2}$ shows that the plasma concentration was decreased through an average of nearly one half-life by 4 hr of perfusion.

**Discussion**

The data demonstrate that hemoperfusion with XAD-4 Amberlite resin removed a significant amount of ethchlorvynol from intoxicated dogs even though the net change in plasma concentration was not striking. It also was shown that drug was removed from RBC's as well as plasma, but that the bulk of removed drug originated from extravascular compartments. Gibson et al [15] demonstrated that digoxin was removed by resin perfusion also from the RBC's of dogs, but that clearance rates between central and peripheral compartments differed with the largest depot equilibrating slowly. In the present study, relatively more drug was left in RBC's than in plasma of outflow samples, supporting the theory of differences in intercompartmental clearance rates. Past perfusion studies often were assessed with an assumption of single compartment behavior and therefore may have overestimated the effect produced.

Column clearances and halflives during perfusion demonstrated that ethchlorvynol was removed at a highly efficient and stable rate through the 4-hr period. The low variability seen particularly in clearance values was striking (Table 2). Koffler et al [22] treated eight ethchlorvynol-intoxicated human patients with fixed-bed charcoal perfusion and observed plasma extraction ratios between 51% and 71% of the plasma flow rate. Five of the eight pa-

**Fig. 3.** *Observed plasma ethchlorvynol concentrations and best-fit line of a single control experiment in which the animal was allowed to detoxify itself through the first biologic half-life.* The best-fit line was fitted to the observed concentrations from 5 to 100 hr.

tients were intoxicated with ethchlorvynol alone. At least two factors could account for the apparent discrepancy between charcoal and resin perfusion: *(1)* the amount of adsorbent available; and *(2)* the adsorption of heparin. The patients of Koffler et al had less than half the amount of adsorbent available to them and probably two or more times the body weight of the dogs. Significant heparin adsorption on charcoal was recently demonstrated [27], but similar studies with resins apparently have not been reported. The use of anticoagulant is unavoidable, and its adsorption would decrease available sites. Competitive differences may exist, however, between the adsorption of heparin, other anti-coagulants, and various depressant drugs, and these may differ from one adsorbent to another.

Teehan et al [28] found a mean biologic $t^{1/2}$ of 72 hr (range, 21 to 105 hr) in four ethchlorvynol-in-toxicated patients. They also observed a mean $t^{1/2}$

**Table 4.** Expression of the net decrease in plasma concentration during perfusion as a proportion of the beginning concentration[a]

| Exp. no. | Plasma ethchlorvynol concentrations | | $P^{1/2}$ |
| --- | --- | --- | --- |
| | $C_{34}$ (B) | $C_{34}$ (A) | |
| | *μg/ml* | | $t^{1/2}$ |
| 1 | 85.4 | 53.8 | 0.668 |
| 2 | 93.8 | 60.2 | 0.641 |
| 3 | 144.2 | 80.1 | 0.849 |
| 4 | 92.2 | 67.7 | 0.445 |
| 5 | 133.0 | 52.1 | 1.352 |
| 6 | 169.5 | 73.9 | 1.197 |
| 7 | 211.6 | 89.6 | 1.240 |
| 8 | 109.8 | 73.1 | 0.587 |
| 9 | 206.4 | 78.3 | 1.398 |
| Mean | 138.4 | 69.9 | 0.931 |
| ± SEM | 16.1 | 4.2 | 0.122 |

[a] Statistical plasma concentrations at the instant hemoperfusion ended ($C_{34}$) are based on the preperfusion (B) and postperfusion (A) lines. $P^{1/2}$ is the number of times the plasma concentration decreased by one half as a result solely of hemoperfusion.

of 21.8 hr (range, 6.3 to 44 hr) during dialysis. In another study involving ethchlorvynol [29], determination of the amount of drug recovered in the dialysis bath and the amount ingested showed that 22.3% was removed from one patient dialyzed for a total of 14 hr, and 32.0% removed from another after 18 hr of dialysis. In comparison, the data in Tables 1 and 2 suggest that resin perfusion removes the drug at a much faster rate than does dialysis and would seem to be more time- and cost-effective.

Rosenbaum et al [10] perfused a patient intoxicated with ethchlorvynol plus glutethimide, butalbital, salicylate, phenacetin, and caffeine for 3 hr. Ethchlorvynol clearances ranged widely from 287 ml/min (95.7% of the whole blood flow rate) to 155 ml/min (51.7%). The XAD-2 resin that was used has a lower capacity than the XAD-4 has [30], and because glutethimide and butalbital also were removed, it is likely that the resin became saturated. It was estimated that 1506 mg of ethchlorvynol was removed even though plasma concentration decreased by only 10 μg/ml. Using the beginning and ending concentrations shown in Table 1 of their report, we calculated a perfusion $t^{1/2}$ and found it to be 8.27 hr, just slightly longer than those of the present study despite the capacity difference between resins. A $P^{1/2}$ also was calculated to be 0.363 $t^{1/2}$'s through the 3-hr perfusion, or 0.483 $t^{1/2}$'s when adjusted to compare with the 4-hr values in Table 4. It was not indicated whether plasma concentration rebounded after perfusion, thus the $P^{1/2}$ may be overestimated. Nevertheless, a greater effect of perfusion may have been realized than the change in plasma concentration alone seems to suggest.

First-order elimination kinetics implies that a decrease in plasma concentration from 300 to 150 μg/ml is quantitatively the same as from 100 to 50 μg/ml because proportionally they are equal. If the time involved in each is the same, the rate of elimination is also proportionally constant, and even

though the net decrease of one is three times the other, the time required to achieve each would be the same. Expression of the effect of perfusion as $P^{1/2}$ (Table 4) describes the decrease in concentration as a proportion in units of a one-half concentration. It characterizes how much of an effect was produced by perfusion when the laws of first-order kinetics are obeyed. In contrast, the half-life indicates the rate of effect. Unlike estimates of the amount removed based on clearance, $P^{1/2}$ should not vary with the beginning or changing concentrations but only with the ongoing rate of elimination which has more bearing on the detoxication being achieved. It therefore can be used to identify dynamic and kinetic factors that alter perfusion effectiveness. It can be applied when preperfusion and postperfusion data are lacking by taking B and A as the concentrations before and after perfusion, respectively. This, however, would include endogenous elimination during perfusion and may exaggerate the effect more if a postperfusion rebound is ignored.

Because endogenous elimination and the postperfusion rebound were taken into account, the decrease described by $P^{1/2}$ (Table 4) is that which is due solely to hemoperfusion. The sizable rebound illustrated in Fig. 1 indicates that the effect of perfusion would have been significantly exaggerated if the rebound had been ignored and thus was a greater source of potential error. The phenomenon of plasma rebound has been observed by others following both dialysis [28] and perfusion [15, 31].

These sources of error may have exaggerated the half-lives, which were determined by established methods. During the constant elimination phase of perfusion, the half-life represented a composite of several rate-discrete processes including metabolism and excretion (which added to the apparent rate of elimination and decreased the half-life), and redistribution from fat and brain tissues (which decreased apparent elimination and increased halflife). If, however, only the rates of redistribution from extravascular compartments are considered, a slower rate would have the misleading effect of decreasing the apparent halflife, assuming a constant rate of removal by perfusion. Both the large initial decrease in concentration at the start of perfusion and the postperfusion rebound may have resulted from a much slower rate of redistribution relative to removal by perfusion. The fact that $P^{1/2}$'s varied widely suggests that redistribution rates may be different for a single drug depending on the predominant body compartment from which it is mobi-

lized, and may be expected to differ between drugs depending on the tightness of binding at sites of action and storage. In the case of fat-soluble drugs, molecules may simply dissolve in lipid tissues and would run out at a rate dependent on blood flow and concentration gradient. Many drugs are subject to both specific and nonspecific binding, however, and in this case the rate of removal may depend at least in part on a competitive relationship between tissue and adsorbent binding characteristics. Thus, the broad usefulness of perfusion in the future may be contingent on a consideration of the chemistry of binding moieties for the purpose of developing adsorbents to be specific and selective for not only drugs but endogenous poisons as well.

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