PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 155, 535-539 (1977)

A Computer Simulation Study Relating to the Treatment of Fulminant Hepatic Failure by Hemoperfusion (39846)

PAUL D. BERK[1]

Section on Diseases of the Liver, Digestive Diseases Branch, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

Introduction. The coma which develops during fulminant hepatic failure has been attributed to either the accumulation of an as yet unidentified toxic metabolite(s) or failure of hepatic production of a substance essential for normal brain function (1). The failure of carefully designed animal cross-circulation experiments mitigates against the latter hypothesis (2), whereas the apparent success of both charcoal hemoperfusion and hemodialysis in promoting arousal from stage IV coma due to fulminant hepatic failure supports the former (3, 4). Furthermore, the tendency of such patients to awaken 12–24 hr after therapy, rather than during the procedure, suggests that arousal results from depletion of the "toxin" from a peripheral pool such as brain or cerebrospinal fluid, which exchanges slowly with plasma (3). A similar delay in arousal has been noted after treatment of comatose patients with chronic liver disease by hemodialysis (5).

In the setting of fulminant hepatic failure, charcoal hemoperfusion is most often applied on a 4-hr per day schedule (3). In the present study, computer simulation techniques were used to investigate whether alternative schedules might more rapidly deplete the apparently critical slowly exchanging extravascular pool of "toxin." Such schedules might accelerate arousal, and thereby improve survival by preventing the cerebral edema and other complications of coma which are the ultimate causes of death in many instances of fulminant hepatic failure, even in patients whose livers are beginning to regenerate (6).

Methods. (*A*) *Rationale.* Since the chemical nature of the hypothetical toxin in fulminant hepatic failure is unknown, it follows that no direct information about its internal distribution and kinetics or about its clearance from blood by artificial support systems is available. However, from the available clinical data, one may speculate that, following removal of the toxin from blood by hemodialysis or hemoperfusion, equilibration with a slowly exchanging extravascular pool occurs at a rate which produces a nadir in the toxin content of this pool at approximately 12–24 hr. This clinical observation is consistent with the known rates of depletion of slowly exchanging pools of neuroactive compounds, such as norepinephrine, from brain (7).

In contrast to the hypothetical toxin accumulating during fulminant hepatic failure, the internal kinetics of unconjugated bilirubin in man have been extensively studied (8), as has its rate of clearance from blood during hemoperfusion with an albumin–agarose "artificial liver" device (9, 10). In addition, unconjugated bilirubin has an extrahepatic, extravascular pool which exchanges slowly with plasma at a rate not inconsistent with that which must also obtain for the hypothetical toxin of fulminant hepatic failure (8). Accordingly, a study of the effects of various albumin–agarose hemoperfusion treatment schedules on the rate of depletion of the extrahepatic extravascular pool of unconjugated albumin has been conducted. It was hoped that this study would provide information which could be applied, by analogy, to assessing the effects of hemodialysis or charcoal hemoperfusion treatment on the slowly exchanging extravascular pool of fulminant hepatic failure toxin. This study in no way implies that accumulation of unconjugated bilirubin plays a role in the production of coma during fulminant hepatic failure.

[1] Address reprint requests to Dr. Paul D. Berk, Liver Unit, DDB:NIAMDD, Bldg. 10, Rm. 4D-52, National Institutes of Health, Bethesda, Maryland 20014.

ISSN 0037-9727

(*B*) *Baseline data.* The initial data on bilirubin pool sizes and fractional transfer rates between pools were from an 18-year-old white female patient with type I Crigler-Najjar syndrome (11), who has been the subject of several previous reports (12–15). A plasma disappearance curve of ^{14}C-labeled unconjugated bilirubin was obtained in this patient over a 12-day period, using previously reported techniques (8). The data were then analyzed on a Univac 1108 digital computer to determine hepatic bilirubin clearance (ml/min/kg), plasma bilirubin turnover (mg/kg/day), and the variables of a previously described (8, 16) and extensively validated (17) three-pool model of unconjugated bilirubin metabolism, using version 27 of the Simulation, Analysis, and Modeling program of Berman and Weiss (18). The results of this analysis are illustrated in Fig. 1.

(*C*) *Simulation of the effects of hemoperfusion.* The effects of albumin-agarose gel hemoperfusion were simulated on the computer by adding an efflux pathway (λ_{01}) to the plasma pool of the model (Fig. 1). The various λ's illustrated are the fractional intercompartmental transfer rates of the model, defined by convention (18) such that λ_{ij} represents the fraction of compartment j transferred per hour to compartment i. While holding the other λ's constant, a subroutine in the program permitted λ_{01} to be altered from 0.0 per hour (no hemoperfusion) to 0.5 per hour (hemoperfusion) and back according to a variety of predetermined schedules. Simultaneously the computer calculated the resulting time course of the plasma unconjugated bilirubin concentration and the bilirubin content of the slowly exchanging extrahepatic, extravascular pool. The value of λ_{01} = 0.5 per hour represents a rate of bilirubin removal sufficient to extract the entire initial bilirubin content of the plasma pool in 2 hr, a rate consistent with the known efficacy of this technique for removing unconjugated bilirubin from the blood of jaundiced experimental animals (9, 10).

Results. The simulated effects over 2 days of a single 4-hr hemoperfusion are illustrated in Fig. 2. During the 4 hr of treatment, the plasma unconjugated bilirubin concentration fell by 60%, from 25 to 10 mg%. At the completion of hemoperfusion, the plasma level promptly began to rise, as a result both of new bilirubin synthesis and reequilibration between intra- and extravascular pools. Predicted plasma bilirubin concentration rose to 15 mg% by 24 hr and, more slowly, to 16 mg% at the end of 48 hr.

In contrast to the plasma pool, the extrahepatic, extravascular bilirubin pool had decreased by only 15% by the end of the 4-hr hemoperfusion period (Fig. 2). However, the bilirubin content of this pool continued to fall after the completion of the perfusion—relatively rapidly over the first 8 hr post-treatment and more slowly over the subsequent 12 hr—as a result of reequilibration with the plasma space. A nadir of 60% of baseline was reached at approximately 24

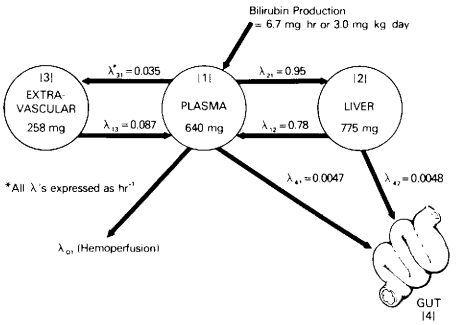

FIG. 1. Compartmental model of unconjugated bilirubin metabolism in a patient with type I Crigler-Najjar syndrome. The figure indicates bilirubin production rate, intercompartmental fractional transfer rates, and steady-state pool sizes determined from study of plasma radiobilirubin kinetics.

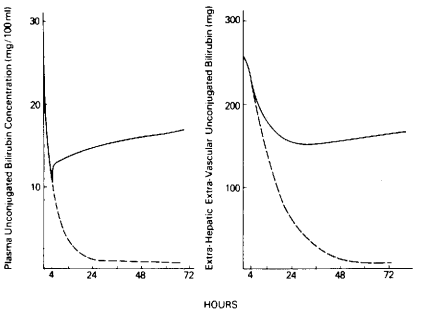

FIG. 2. Computer-simulated effects of a single 4-hr hemoperfusion (solid line) or continuous hemoperfusion (dashed line) on plasma and extrahepatic, extravascular bilirubin in a patient with type I Crigler-Najjar syndrome.

hr after initiation of the procedure, consistent with the time course of arousal of comatose patients with fulminant hepatic failure after charcoal hemoperfusion therapy.

The simulated results of several alternative hemoperfusion schedules over a 5-day period are illustrated in Fig. 3. Continuous hemoperfusion, a clinically impractical regimen, was the most efficient, reducing the plasma unconjugated bilirubin concentration to 1.2 mg% and the extrahepatic, extravascular bilirubin pool to values within the normal range (<65 mg) (8) by 24 hr. In contrast, the usually employed regimen of 4 hr of treatment per day, while reducing the plasma bilirubin concentration with each treatment, did not achieve plasma bilirubin values consistently under 6 mg% until after the fourth treatment. Similarly, the extrahepatic, extravascular pool did not reach the normal range until the fourth treatment, more than 72 hr after initiation of therapy.

To the extent that earlier normalization of the toxin content of the slowly exchanging extrahepatic, extravascular pool might improve survival, the data in Fig. 2 suggest two manipulations in the regimen which might be beneficial. One involves prolonging the initial perfusion. Thus, Fig. 3 indicates that initial perfusions of either 12 or 24 hr, followed by maintenance treatments of 4 hr daily, will achieve normalization of the extrahepatic, extravascular pool within 28 and 24 hr, respectively, of initiating treatment, and that this result will be sustained by the 4 hr per day maintenance regimen.

Alternatively, because the decline in the toxin content of the slowly exchanging extravascular pool tends to slow asymptotically toward zero following each perfusion, repetitive short perfusions at intervals of less than 24 hr will also accelerate depletion of toxin from this pool. This approach is illustrated in Fig. 4. Thus, two perfusions of 6 hr each, at the start of treatment and at 12 hr, will result in normalization of the slowly exchanging extravascular pool by 30 hr. Merely adding a single additional 4-hr treatment at 12 hr into the conventional 4 hr per day regimen achieves normalization of this pool by 44 hr, a saving of more than a full day in the time required to normalize this variable.

Discussion. The results presented above suggest that albumin-agarose hemoperfusion could reduce the plasma unconjugated bilirubin concentration substantially and the extrahepatic, extravascular bilirubin pool size to within normal limits in patients with type I Crigler-Najjar syndrome. Moreover, the rate at which normalization of these variables is achieved is dependent not only on the efficiency of the device employed, but also on the treatment schedule. It is suggested, by analogy, that the treatment schedule employed in the treatment of fulminant hepatic failure by charcoal hemoperfusion may be equally important in determining the rate at which the hypothetical "toxin" in that condition is depleted from its

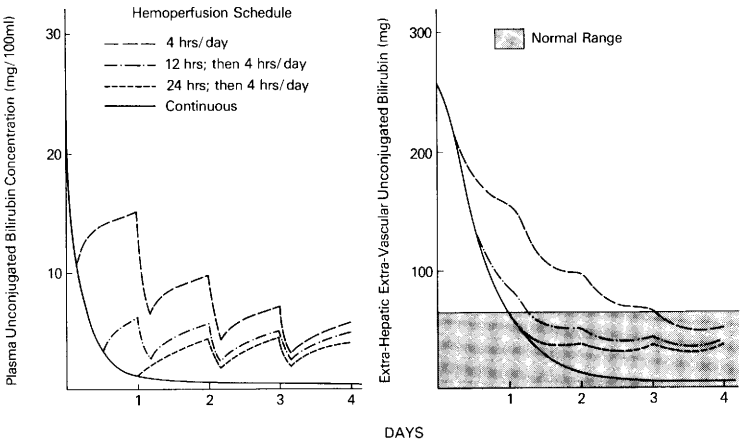

FIG. 3. Computer-simulated effects of four different treatment schedules on plasma and extrahepatic, extravascular bilirubin pools in type I Crigler-Najjar syndrome.

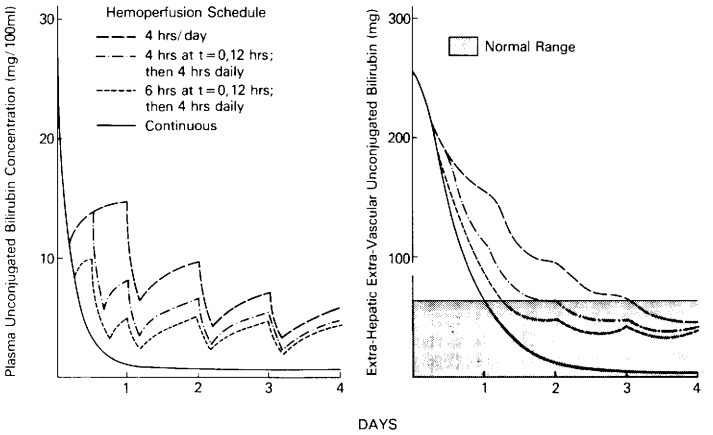

FIG. 4. Computer-simulated effects of additional treatment schedules on plasma and extrahepatic, extravascular bilirubin pools in type I Crigler-Najjar syndrome.

slowly exchanging extravascular sites.

The validity of this study is dependent on several sets of assumptions. The first involves basic biological considerations: for example, that coma in fulminant hepatic failure is indeed the result of the accumulation of toxic substances in a critical compartment which equilibrates slowly with the bloodstream. This hypothesis, while by no means proven, is consistent with the majority of available evidence (1), although neither the nature of the toxin nor the site of the critical pool to be depleted is certain. The second set of assumptions is mathematical: for example, that the distribution of a metabolite among kinetically distinct pools can be described by a compartmental model, that the transfer rates of the model are independent of pool sizes (first-order kinetics), and that, accordingly, baseline values for the parameters of the model can be used to predict the effects of perturbations such as hemoperfusion. The model of bilirubin kinetics employed in this study has been extensively validated in both published studies in man (8, 17) and unpublished data obtained in the rat (19). The first-order nature of bilirubin transfer between critical pools is suggested by the similarity of the transfer rates representing hepatic uptake (λ_{21}) and, more relevant to the present study, return from the slowly exchanging extrahepatic, extravascular pool to plasma (λ_{13}) in normal subjects and patients with Crigler-Najjar syndrome (8, 11, 14, 16). The ability of computer simulations involving other compartmental models to accurately predict the effects of physiologic perturbations has been previously demonstrated (15). Furthermore, the predicted time course of the plasma bilirubin concentration curve during the initial perfusion in the present study is virtually superimposable on the curve actually observed in the same patient when an equivalent rate of bilirubin clearance was obtained by exchange plasmapheresis during an episode of bilirubin encephalopathy (14). Qualitatively similar plasma curves have been observed during and after hemoperfusion of jaundiced monkeys (10), although lack of data on the internal kinetics of bilirubin in the monkey precludes direct comparison of these data with computer-simulated curves.

This study clearly emphasizes the ignorance of basic pathophysiology which surrounds current efforts to devise new therapies for fulminant hepatic failure. Just as an understanding of cell cycle kinetics led to new regimens which dramatically improved the effectiveness of known drugs in acute lymphoblastic leukemia (20), understanding of the specific biochemical disturbances requiring correction might lead to regimens which would dramatically improve survival in fulminant hepatic failure with existing therapeutic modalities.

Simple alterations in treatment schedule such as the addition of one additional 4-hr hemoperfusion or, preferably, use of two 6-hr perfusions during the first day may markedly accelerate depletion of a slowly equili-

brating extravascular pool of toxin in fulminant hepatic failure. This might be expected to accelerate arousal, prevent the cerebral edema associated with prolonged acute hepatic coma (6), and thereby improve survival. Although these are the results of a theoretical investigation, they leave workers in this largely empirical field with a rationally derived and readily testable hypothesis.

Summary. A lag period of 12–24 hr has frequently been observed to elapse between charcoal hemoperfusion therapy and arousal of patients in stage IV coma due to fulminant hepatic failure. This delay suggests that recovery of consciousness depends on depletion of an extravascular pool of a hypothetical toxin which requires 12–24 hr to equilibrate with plasma. No further definitive information about the nature of the toxin is available. Unconjugated bilirubin is known to have an extrahepatic, extravascular pool which also equilibrates with plasma over a 12- to 24-hr period. Accordingly, a model of unconjugated bilirubin kinetics has been used to investigate the rate of depletion of slowly equilibrating extravascular metabolic compartments by hemoperfusion, employing computer simulation techniques. The results indicate that the rate of depletion of slowly equilibrating extravascular pools is critically dependent not merely on the intrinsic efficiency of the hemoperfusion device, but also on the schedule with which it is employed. The conventionally employed regimen of 4-hr of treatment per day is relatively inefficient in achieving depletion of such compartments. These data imply, by analogy, that alternative hemoperfusion regimens, employing longer initial perfusion or perfusions at intervals of approximately 12 hr, would be more effective than current schedules in awakening patients with acute hepatic coma.

The author is indebted to Ms. P. Cromwell for assistance with this study and for preparation of the manuscript.

1. Schenker, S., Breen, K. J., Hoyumpa, A. M., Jr., Gastroenterology **66,** 121 (1974).
2. Roche-Sicot, J., Sicot, C., Peignoux, M., Bordiau, D., Degos, F., Degos, J. D., Prondi, D., Rueff, B., and Benhamou, J-P., Clin. Sci. Mol. Med. **47,** 609 (1974).
3. Gazzard, B. G., Weston, M. J., Murray-Lyon, I. M., Record, C. O., and Williams, R., *in* "Artificial Hepatic Support" (R. Williams and I. M. Murray-Lyon, eds.), p. 234. Pitman, London (1974).
4. Opolon, P., Rapin, J-R., Huguet, C., Granger, A., Delorme, M-L., Boschat, M., and Sausse, A., Trans. Amer. Soc. Artif. Int. Organs **22,** 701 (1976).
5. Kiley, J. E., Pender, J. C., Welch, H. F., and Welch, C. S. N. Engl. J. Med. **259,** 1156 (1958).
6. Gazzard, B. G., Portmann, B., Murray-Lyon, I. M., and Williams, R., Quart. J. Med. **44,** 615 (1975).
7. Glowinski, J., Kopin, I. H., and Axelrod, J., J. Neurochem. **12,** 25 (1965).
8. Berk, P. D., Howe, R. B., Bloomer, J. R., and Berlin, N. I., J. Clin. Invest. **48,** 2176 (1969).
9. Scharschmidt, B. J., Plotz, P. H., Berk, P. D., Waggoner, J. G., and Vergalla, J., J. Clin. Invest. **53,** 786 (1974).
10. Scharschmidt, B. F., Martin, J. F., Shapiro, L. J., Plotz, P. H., and Berk, P. D., J. Lab. Clin. Med. **89,** 101 (1977).
11. Berk, P. D., Berlin, N. I., and Howe, R. B., *in* "Diseases of Metabolism" (P. K. Bondy and L. Rosenberg, eds.), pp. 825–880. Saunders, Philadelphia (1974).
12. Childs, B., and Najjar, V. A., Pediatrics **18,** 369 (1956).
13. Childs, B., Sidbury, J. B., and Migeon, C. J., Pediatrics **23,** 903 (1959).
14. Blaschke, T. F., Berk, P. D., Scharschmidt, B. F., Guyther, J. R., Vergalla, J. M., and Waggoner, J. G., Pediat. Res. **8,** 573 (1974).
15. Berk, P. D., Scharschmidt, B. F., Waggoner, J. G., and White, S. C., Clin. Sci. Mol. Med. **50,** 333 (1976).
16. Bloomer, J. R., Berk, P. D., Howe, R. B., and Berlin, N. I., Pediat. Res. **5,** 256 (1971).
17. Berk, P. D., *in* "Jaundice" (M. M. Fisher and C. A. Goresky, eds.), pp. 135–137. Plenum Press, New York (1975).
18. Berman, M., and Weiss, M. F., U. S. Public Health Service Publication. 1703. U. S. Government Printing Office, Washington, D. C. (1967).
19. Scharschmidt, B. F., Berk, P. D., and Waggoner, J. G., J. Clin. Invest. **21,** 523 (1973) (abstract).
20. Henderson, E. S., *in* "Cancer Medicine" (J. F. Holland and E. Frei, III, eds.), pp. 1173–1199. Lea & Febiger, Philadelphia (1973).

Received March 18, 1977. P.S.E.B.M. 1977, Vol. 155.