Table I—Comparison of Methods of Estimating the Fraction of Sotalol in the Body Removed by Hemodialysis [a]

Time of Dialysis, hr	AUC_1, mg/liter/hr	AUC_2, mg/liter/hr	f Eq. 1	f Eq. 4	f Eq. 5
1–7	5.87	6.77	0.17	0.26	0.26
12–18	1.75	3.67	0.17	0.20	0.20

[a] Pharmacokinetic parameters taken from Refs. 3 and 4; Cl = 140 ml/min, V = 136 liters, and Cl_D = 105 ml/min, with an intravenous bolus dose of 160 mg.

plasma concentration–time curve from the termination of EDR to infinity.

The fraction of drug in the body at the start of EDR that is removed by the device is given by:

$$f = \frac{X_D}{X_S} \qquad \text{(Eq. 4)}$$

which, from Eq. 3, may be expressed as:

$$f = \frac{Cl_D AUC_1}{(Cl + Cl_D)AUC_1 + ClAUC_2} \qquad \text{(Eq. 5)}$$

To test the validity of Eq. 5, plasma concentrations of sotalol, a β-adrenergic receptor blocking agent, were simulated by computer. Pharmacokinetic parameters describing the time course of this drug in the body were obtained from Sundquist *et al.* (3). Hemodialysis was started and terminated at 1 and 7 hr, respectively, following intravenous bolus administration. In a second simulation, dialysis was started and terminated at 12 and 18 hr following drug administration. A dialysis clearance, Cl_D, for sotalol of 105 ml/min was estimated from the study by Tjandramaga *et al.* (4). Areas under the plasma concentration–time curve were estimated using the trapezoidal rule.

By employing Eq. 4, f was determined directly using the simulated amounts in the plasma and tissue compartments at the beginning of dialysis, X_S, and the amount of drug removed by dialysis, X_D. The value of f obtained was compared with that obtained using Eqs. 1 and 5 (Table I).

Sotalol pharmacokinetics can be described by a two-compartment model with a distribution phase of ~10 hr. When dialysis is performed during the distribution phase of the drug, use of Eq. 1 underestimates the fraction of drug removed by dialysis. When dialysis is conducted in the postdistributive phase, the prediction of f using Eq. 1 improves but still underestimates this parameter. Regardless of the time of dialysis relative to drug administration, Eq. 5 accurately predicts the fraction of drug removed from the body.

Equation 5 provides a valid means of determining the fraction of drug removed by EDR. It is more general than Eq. 1 in that it can be applied to drugs following multicompartment pharmacokinetics regardless of the time of EDR relative to drug administration. The clearance values are easily obtained. Proper use of the equation requires that the final plasma sample be obtained during the terminal log-linear phase of the plasma drug concentration curve and that the slope of this linear phase be determined to estimate AUC_2 accurately.

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Peter R. Gwilt
School of Pharmacy
Ferris State College
Big Rapids, MI 49307

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Novel Source of Ubiquitous Phthalates as Analytical Contaminant

Keyphrases □ Plasticizers—phthalate, analytical contaminant □ Mass spectrometry—detection of phthalate esters by selected-ion monitoring □ Phthalates—interference with oxprenolol assay using GLC with electron-capture detection □ Contaminants—phthalates, interference in drug assays using electron-capture detection

To the Editor:

The ubiquitous distribution of the phthalate ester plasticizers in the environment is well known, and they are frequently encountered in samples processed in biomedical laboratories. Although the analyst can often identify phthalate plasticizers in biological samples, it is not always clear whether the plasticizer is a genuine contaminant in the specimen or an analytical artifact (1). Phthalates are readily leached into blood stored in plastic containers (2), and collecting blood specimens with evacuated tubes (3) or some plastic syringes (1) can result in contamination with phthalates or other plasticizers.

In addition to their ubiquity, the phthalates manifest two other frustrating properties for the analyst. First, the range of phthalate esters used commercially ensures that a phthalate will cochromatograph with many analytes of interest such as barbiturates (4), disopyramide (5), and long-chain fatty acids (6). Second, although the phthalate esters contain no halogen atoms, they show good response factors to the electron-capture detector (7), which ensures that even nanogram quantities may interfere in trace level determinations of some compounds.

The range of reported sources of phthalates as analytical contaminants is impressive, but we recently encountered a novel and unexpected source that could be of importance to analysts using electron-capture detection for trace level assay of drugs.

To carry out low dose bioavailability studies with oxprenolol, a sensitive assay for this β-blocking drug in plasma was required. An assay by GLC with electron-capture detection, using heptafluorobutyryl derivatives of oxprenolol and the internal standard (metoprolol), was investigated. However, assay blanks invariably contained a spurious peak with a retention time almost equivalent to that of derivatized oxprenolol. A phthalate plasticizer was suspected, so meticulous care was taken to ensure that no plastic materials came in contact with any glassware, reagents, or specimens used. The contaminant persisted, and one of the offending blanks was subjected to GLC–mass spectrometric analysis to confirm the presence of the suspected phthalate. No confirmation could be established

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when the mass spectrometer was operated in the full-scan mode. However, when the sample was analyzed in the more sensitive selected-ion mode, with the mass spectrometer focussed only on ions of mass 149 and 167, which are prominent in the spectrum of bis(2-ethylhexyl) phthalate (8), the presence of this compound was indicated.

Careful reassessment of the entire oxprenolol assay revealed that the only plastic material used was about 2 m of polyvinyl chloride tubing attached to a Pasteur pipet; it was employed to blow nitrogen over the tubes in a water bath for solvent removal. When this polyvinyl chloride tubing was replaced with polytetrafluoroethylene tubing, clean blanks were achieved.

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Wayne D. Hooper ˣ
Maree T. Smith
Department of Medicine of Queensland University
Royal Brisbane Hospital
Herston Qld 4029, Australia

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Effects of Spermine and Spermidine on Gastric Emptying in Rats

Keyphrases □ Spermine—effects on gastric emptying in rats, structure–activity relationships □ Spermidine—effects on gastric emptying in rats, structure–activity relationships □ Structure–activity relationships—spermidine and spermine, effects on gastric emptying in rats

To the Editor:

Spermine and spermidine have been intensively studied with regard to their function in cellular metabolism and, more recently, their role in normal and neoplastic growth (1). These biogenic amines were reported (2) to occur in relatively high concentrations in the GI tract, but no precise physiological role has been attributed to them.

Recently, we reported that a branched-chain polyethyleneamine (mol. wt. >600) greatly inhibited gastric emptying in the rat while an isomeric linear version of this same polymer was essentially inactive (3). Since the repeating unit in both branched and linear polyethyleneimine is somewhat similar to that of spermine and spermidine, we decided to measure the effect of spermine, spermidine, and related small molecule polyamines on the stomach emptying rate in the rat.

Table I—Effects of Polyamines on Gastric Emptying in the Rat

Compound	Molecular Weight	Dose, mg/kg po	Inhibition at 4 hr, %[a]
Diethylenetriamine	103	250	0
Triethylenetetramine	146	250	0
N,N^1-Bis(3-aminopropyl)piperazine	200	250	23
(*N*-Aminoethyl)-1,4-diaminobutane	131	250	36
Spermidine	145	250	87
Polyethyleneimine (commercial product)	>40,000	250	92
Polyethyleneimine (linear)	>10,000	250	11

[a] Resin bead method; see Ref. 3

The results of initial studies (Table I) indicate that the naturally occurring polyamines, spermine and spermidine, are highly effective in reducing gastric emptying in the rat. Certain closely related commercially available polyamines, such as diethylenetriamine and triethylenetetramine, are completely inactive. Other analogs such as (*N*-aminoethyl)-1,4-diaminobutane and N,N^1-bis(3-aminopropyl)piperazine have weak activity.

The structure–activity (inhibition of gastric emptying) of these compounds may be summarized as follows:

$$H_2N(CH_2)_mNH(CH_2)_nNH(CH_2)_mNH_2$$

$m = 3, n = 4$ spermine (very active)
$m = 2, n = 2$ triethylenetetramine (inactive)

$$H_2N(CH_2)_mNH(CH_2)_nNH_2$$

$m = 3, n = 4$ spermidine (very active)
$m = 2, n = 4$ *N*-aminoethyl-1,4-diaminobutane (low activity)
$m = 2, n = 2$ diethylenetriamine (inactive)

$m = 3$ N,N^1-bis(3-aminopropyl)piperazine (low activity)

These results indicate that gastric emptying inhibition in the rat by both polymeric and low molecular weight polyamines is clearly dependent on chemical structure. The reason for this structural specificity is not known. The results suggest, however, that endogenous spermine and spermidine may have some unrecognized GI secretomotor activity that can be duplicated by conformationally similar synthetic materials.

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E. J. Belair *
G. R. Carlson
S. Melamed
J. N. Moss
Research Laboratories
Rohm and Haas Company
Spring House, PA 19477
M. F. Tansy ˣ
Department of Physiology and Biophysics
Health Sciences Center
Temple University
Philadelphia, PA 19140

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* Present address: Adria Laboratories, Columbus, OH 43216.