From these studies, it is clear that the availability of intracellular calcium is a factor in the defense mechanism of inflammatory cells in *L. donovani* infections.

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Concentration of ibuprofen in cervical mucus

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Abstract—Concentrations of an acidic drug, ibuprofen, in cervical mucus and serum have been measured by HPLC after oral administration in six healthy volunteers. After an 800 mg single dose of ibuprofen, the concentration reached in cervical mucus was less than 4% of that in serum. It is postulated that because ibuprofen is an acidic drug which is not subject to 'ion-trapping' in the acidic environment of cervical mucus, it is not concentrated in this secretion.

Studies on drug disposition in cervical mucus are important for at least two reasons. Firstly drugs may exert their therapeutic action through their concentration in the genital tract, for example metronidazole in the treatment of Trichomonas infections (Fleury et al 1977). Secondly, drugs may exert unwanted effects, for example reducing sperm motility and fertility. Propranolol has been shown to be concentrated in cervical mucus (Pearson & Ridgway 1985) and to reduce sperm motility in-vitro (Hong et al 1981).

Little is known, however, of those physicochemical properties of a drug which determine its penetration into the female genital tract. Basic drugs such as propranolol have been shown to concentrate forty fold in cervical mucus after oral administration (Pearson & Ridgway 1985). The disposition of acidic drugs in cervical mucus has not been studied. We have examined the concentration of a widely used acid drug, ibuprofen, in cervical mucus and serum with a view to identifying those factors influencing the secretion of drugs into cervical mucus. Ibuprofen is acidic (pK_a 5), moderately lipophilic and is 99% bound to serum proteins (Albengres et al 1988). It is readily and almost entirely absorbed after oral administration (Moffat 1986) and is inactivated and/ or eliminated by biotransformation, the liver fulfilling the main role in its total body clearance. Studies on its distribution in other bodily fluids have shown that the ratio of its concentration in synovial fluid compared with plasma was about 1·25 after a single dose with a similar value obtained at steady state (Netter et al 1989). In a case report, negligible levels ($< 0{\cdot}05$ $\mu g\ mL^{-1}$) of ibuprofen and its metabolites were reported in the breast milk of lactating women after 17 days of therapy with 400 mg tablets of ibuprofen twice a day (Weibert et al 1983).

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Materials and methods

Subjects and experimental design. Six healthy female volunteers, aged 21–23 (mean 21·3) years and weighing 57·2–72·0 (mean 65·2) kg, took a single dose of 800 mg (2 × 400 mg tablets) ibuprofen (Boots Co. plc) by mouth at 0800 h on the study day after overnight fasting. They attended on day 14 of the menstrual cycle when the cervical mucus is most prolific. None were using hormonal contraceptives or intrauterine devices. All were non-smokers, drug-free and abstained from sexual intercourse for two weeks before and during the study. None had significant abnormal findings on clinical examination, plasma biochemistry, urinalysis or was pregnant. All volunteers were informed of the design and aims of the study and gave written consent. This study was approved by the City and Hackney District Health Authority Ethics Committee.

Sampling procedures. Samples of cervical mucus were taken from the upper vagina and posterior fornix before (0) and at 0·5, 1, 2, 4, 6, 8, 10 h after the 800 mg dose of drug. This was done using the sterile volumetric vaginal aspirator (Ovumeter) described by Usala & Schumacher (1983). The samples were transferred to pre-weighed vials and then re-weighed before analysis. Blood samples from an antecubital vein were taken at the same times and placed in plain glass tubes, left to clot and serum separated by centrifugation (10 min, 3000 rev min^{-1}). Serum and cervical mucus samples were stored at −20°C until assayed.

Drug concentrations in cervical mucus and serum were determined by HPLC using an adaptation of the method of P. J. Street, National Poisons Unit, New Cross Hospital, London (personal communication). Mucus was diluted in 0·25 mL of phosphate buffered saline before assay. Using 100 μL serum or cervical mucus, the sensitivity of the method was in the range of 200–1000 ng L^{-1}. The reproducibility was within ±9·8% at the lower limit of detection.

Statistical and pharmacokinetic calculations. Half-life ($t_{\frac{1}{2}}$), peak concentration (C_{max}) and the area under the drug concentration-time curve (AUC) were calculated using a microcomputer program STRIPE (Johnston & Woollard 1983). Student's paired *t*-test (two-tailed) was used for analysis of significant differences between cervical mucus and serum phamacokinetic variables (C_{max}, AUC, $t_{\frac{1}{2}}$) of ibuprofen. Wilcoxon's (1945) signed rank sum test was used to analyse non-parametric data, the time to reach the peak (t_{max}) in cervical mucus and serum. 95% confidence intervals (95% CI) for means and their differences were calculated. The statistical methods used are described in Armitage (1987). *P* values <0·05 were considered to be significant.

Results

Samples were successfully obtained at each sample time from all subjects; there were no adverse reactions. After 800 mg single oral dose, the mean maximal level of ibuprofen in cervical mucus increased from zero to 1·49±0·6 mg kg^{-1} at 6 h and fell to 0·17±0·02 mg kg^{-1} at 12 h. The concentration of ibuprofen in serum increased rapidly, reaching a mean maximum of 52·7±5·0 mg L^{-1} at 2 h, and then declined to 9·7±0·9 mg L^{-1} at 6 h, followed by a slow decline to 1·4±0·2 mg L^{-1} at 12 h.

The individual pharmacokinetic variables for ibuprofen in cervical mucus and serum are given in Table 1. The time to reach the peak (t_{max}) in cervical mucus was significantly greater than that in serum with an estimated median of 3·5 h (95% CI 2·0 to 5·0, $P<0·05$). The peak concentration (C_{max}) in cervical mucus was significantly less than that in serum with a mean difference of −53 mg L^{-1} (kg) (95% CI −65 to −40, $P<0·01$). The area under the curve for cervical mucus was significantly less than that in serum, with a mean difference of −204 mg L^{-1} (kg) h (95% CI −237 to −171, $P<0·01$). The elimination half-life in cervical mucus was significantly less than that in serum with a mean difference of −0·6 h (95% CI −1·1–0·11, $P<0·05$).

Discussion

The extent to which a drug and its metabolites appear in human body fluids depends on several factors including lipid solubility, protein-binding and dissociation constant (pK_a). In this study after a single 800 mg oral dose of ibuprofen, the concentration reached in cervical mucus was very low in relation to serum. The low levels of protein in cervical mucus present during the mid-cycle (Schumacher 1973; Chantler & Elstein 1986) could be one factor that might explain this finding. However, basic drugs such as propranolol, which is lipid-soluble, and atenolol which is water-soluble, reached higher concentrations in cervical mucus than in serum during mid-cycle (Salas et al 1989, 1990). Thus it is the drug pK_a rather than the concentration of protein in cervical mucus, or lipid-solubility of a drug that seems to be the important factor involved in the accumulation of drug in cervical mucus. This observation is consistent with studies on sulphamethoxazole-trimethoprim and ofloxacin (Tartaglione et al 1988) and erythromycin (Iliopoulou et al 1981) which indicated that basic compounds are concentrated in acidic fluids such as vaginal secretions at levels greater than in blood. However, for weak acidic drugs such as ibuprofen, there is no concentration into cervical mucus since there is no "ion trapping" in the acidic environment of cervical mucus.

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Table 1. The individual pharmacokinetic variables for cervical mucus and serum following an 800 mg oral dose of ibuprofen in healthy volunteers.

	Cervical mucus				Serum			
Subject no.	t_{max} h	C_{max} mg kg^{-1}	$t_{\frac{1}{2}}$ h	$AUC_{0-\infty}$ mg kg^{-1} h	t_{max} h	C_{max} mg L^{-1}	$t_{\frac{1}{2}}$ h	$AUC_{0-\infty}$ mg L^{-1} h
1	4	2·2	1·2	17·1	2	45·7	1·1	222·7
2	4	1·8	0·8	15·4	2	50·3	1·6	206·1
3	6	4·2	0·6	17·9	1	55·5	1·8	204·0
4	6	0·7	1·4	3·7	2	61·6	1·7	233·9
5	6	0·8	1·4	6·2	1	42·1	2·0	168·0
6	4	0·5	0·9	3·0	2	72·8	1·8	251·4
mean	6*	1·7	1·0	10·5	2*	54·7	1·7	214·3
s.e.m.	4-6*	0·6	0·1	2·8	1-2*	4·6	0·1	11·7

* Median and range.

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Book Review

Analysis for Drugs and Metabolites, Including Anti-infective Agents
Edited by E. Reid and I. D. Wilson
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Every two years, alternating with a similar forum on biochemistry, Guildford Academic Associates organizes a Bioanalytical Forum at the University of Surrey and this book is the result of the eighth meeting in the series. Like the preceding seven volumes the present volume has an unwieldly title, apparently to provide a unique title in the publisher's list. However, the subtleties of the titles can be safely ignored, the value of the forum being in getting together European, if not world, experts to exchange experiences and report advances in the difficult science or art of bioanalysis.

The present book is divided into three more or less equal parts. Part A (Producing Valid and Acceptable Results) is a very timely and up-to-date exposition of the various criteria that are used by the analytical laboratories to persuade their clients (whether in-house or contract) that their reported results can be relied upon. In the late twentieth century climate of government regulation the importance of a standardized approach and nomenclature warrants the extensive discussion supplied here. The review by Dell on the practices adopted by different laboratories indicates that bioanalysts are indeed starting to come to some consensus on the presentation of analytical results.

Part B (Anti-infective Drugs and their Metabolites) comprises mainly analytical methods for named drugs and their known metabolites. Although anti-infective drugs are used as the common thread, the range of approaches used means the section can be of general interest also.

Part C (Approaches for Various Drugs and their Metabolites) provides a carte blanche for analysts to present new methodology, as opposed to old methodology for new drugs, and in some cases to allow flights of fancy for the future direction of bioanalysis.

A feature of these meetings is the discussion periods on what are in fact very practically-oriented issues, and this feature has been carried faithfully into the books. I must declare an interest here; I have attended all these meetings since their inception in 1975, but this was the first I had been unable to attend throughout. I was therefore interested to see if the discussions would appear as alive in cold print to the non-participant and indeed I did feel that the spirit of the discussions is captured in these pages.

If memory serves me right, this book has been produced much more quickly after the Forum than any of its predecessors and without as far as I could see any typographical errors; the editors should be congratulated on this. Recalcitrant authors who did not come up with final manuscripts do not escape unreported, with the editors salvaging their contributions from advance abstracts and records of the discussions. Indeed the hand of the Senior Editor is evident throughout; authors are allowed to have their say but unclear or contradictory statements are not allowed to go by without comment. Extra pertinent references are added by the Editor with notes cross-referencing other articles and even other volumes in the series. The result is not always pretty, but the attention to detail is impressive.

It would be perhaps, more useful if the index followed conventional lines, rather than a scheme of the Editor's own. Although this scheme may appear logical it requires the reader to learn it before he can use it. Another quibble on the indexing is that it is not always possible to determine the affiliation of speakers in the discussion unless they also appear as a co-author at the meeting.

All in all though, this is an extremely useful book for the practical analyst, whether already experienced in the field or a newcomer trying to learn the tricks of the trade.

JOSEPH CHAMBERLAIN