


Antimicrobial drugs in human seminal plasma

The penetration of drugs into the human male genital organs is an almost unexplored field. It is known that alcohol, antibiotics and some other drugs can be recovered from semen after oral administration (Mann, 1972). Excretion of antibacterial drugs into human semen has been studied by only a few investigators. When Armstrong, Cook & Robinson (1968) published a study on the concentration of 15 antimicrobial drugs in the ejaculum they also made a review of the literature on antibiotic concentrations in human male genital organs. The list contained only 8 articles. Most previous pharmacokinetic studies on the excretion of drugs into the reproductive tract have been carried out on dogs (Applington & Silver, 1967; Winningham, Nemoy & Stamey, 1968; Hessl & Stamey, 1971; Robb, Carroll, Tippett & Langston, 1971; Granato, Gross & Stamey, 1973). The scarcity of information gained from human studies has led many scientists to make their deductions from these dog experiments. The marked anatomical, chemical and physiological differences between the reproductive organs of various species should be given more consideration. In contrast to man, canine seminal plasma originates almost exclusively from the prostate as the dog is a species lacking vesicular glands. The human seminal plasma is a composite mixture of secretions from the various accessory genital glands. The constituents of semen come from 3 organs. The testes produce spermatozoa, the seminal vesicles excrete fructose and the prostate excretes acid phosphatase, citric acid and zinc. In healthy males about 30% of seminal plasma originates from the prostate, approximate 60% from the seminal vesicles and the remainder from the epididymis, ampullae, bulbo-urethral and urethral glands.

Biochemical analysis of human seminal plasma can give objective and valuable information about the secretory function of the accessory genital glands. The origin of a compound present in the seminal plasma can be studied by using the split ejaculate technique, first described by Lundqvist (1949). The semen samples are obtained by masturbation. The man is instructed to collect the ejaculate in a tray containing six boxes in such a way that the first portion of the ejaculate is caught in box number 1, the second in box number 2, etc. Most men can split the ejaculate into four to six fractions. Each fraction is then analysed for acid phosphatase and zinc, specific for the prostate fluid, fructose, specific for the vesicular fluid, and for the factor under study. Unfortunately there do not yet exist any accepted markers for the fluids originating from the epididymis, ampullae ductus deferens and the bulbo-urethral glands.

Although some investigators have looked at the excretion of antimicrobial drugs in human semen the pharmacokinetic studies have not been so careful. As for example, Armstrong et al. (1968) did not report the time interval between drug intake and the delivery of semen samples. Experiments with split ejaculates have given more accurate information about the pharmacokinetics of some antimicrobial drugs seminal plasma. After single oral doses (700 mg) of pivampicillin to healthy men the maximum concentration (mean 2.2 µg/ml) in seminal plasma was reached 4 to 5 h after drug intake. The level was closely related to the zinc concentration indicating that ampi-
cillin is mainly excreted from the prostate (Malmborg, Dornbusch, Eliasson & Lindholmer, 1975). Studies with doxycycline have shown that the maximum levels (mean 2.0 ug/ml) were reached 4 to 6 h after the dose of 200 mg. The decline was directly proportional to that of zinc, which indicated that doxycycline also originated mainly from the prostate gland (Eliasson & Malmborg, 1976).

Winningham, Nemoy & Stamey (1968) showed that a close relationship existed between the dissociation constant ($pK_a$) and lipid solubility of drugs and their penetration into the prostatic fluid. The hydrogen ion concentration was also important for the excretion. They used a special equation (Henderson-Hasselbach) to illustrate their findings theoretically. When Eliasson & Dornbusch (1977) studied the excretion of trimethoprim (TMP) they found that similar amounts of TMP were excreted by both the prostate and the seminal vesicles. They tried to explain this finding with the same calculations as Winningham et al. (1968). TMP has a $pK_a$ of 7.3. If the prostatic fluid is acid, pH 6.6 and the vesicular fluid basic, pH 7.8, the TMP concentration in the prostatic fluid should be approximately four times that in the vesicular fluid. But if the fluids of the prostate and the seminal vesicles both have a pH between 7.4 and 8.0 there should be the same TMP concentration in both fluids. In a later study (Eliasson, Malmborg, Dornbusch & Kvist, 1978) the pH was measured in the various fractions of split ejaculates. The mean in the first (prostatic) fraction was 7.8 (range 7.4 to 8.4) and the mean in the last (vesicular fluid) fraction was 8.1 (range 7.7 to 8.6). These findings reinforce the results of the study with TMP.

Erythromycin is a basic macrolide with a $pK_a$ of 8.9. Its activity is known to increase with increase of pH. Studies with split ejaculates (Eliasson et al., 1978) showed that the ratio between concentration in the blood plasma and the first fraction of the split ejaculate (i.e. more or less the prostatic fluid) was on the average 0.97 with a range from 0.69 to 1.4. Maximum levels (mean 1.4 ug/ml) were obtained 4 to 6 h after intake of 500 mg erythromycin. After 24 h concentrations were still found (mean 0.4 ug/ml). The secretory pattern showed that the concentration followed that of zinc indicating that erythromycin was mainly secreted by the prostate.

Sulphonamides have been shown to not penetrate significantly into the prostate gland of dogs. Winningham & Stamey (1970) and Robb, Carroll, Tippitt & Longston (1971) found a plasma concentration of sulphamethoxazole (SMZ) 10 times higher than that of prostatic fluid. However, Eliasson & Dornbusch (1977) found high concentrations of SMZ in the semen from three patients. The concentrations were 34, 72 and 92% respectively of those in the blood plasma. Oosterlinck, Defoort & Renders (1975) found after 4 days that the concentration of SMZ was sufficient to obtain synergism with TMP against many micro-organisms. Eliasson & Dornbusch (personal communication) have also made pharmacokinetic studies of metronidazole. The drug did not show a homogenous excretion pattern in the different split ejaculates. In most cases the pattern indicated that the main part was excreted through the prostate gland but further studies seem necessary to clarify the various factors that may influence the excretion.

Adequate concentrations of active antimicrobial drugs in the organs producing the semen are important in the medical management of infections in these glands. More pharmacokinetic studies on the excretion of established and new antimicrobial drugs into human male genital glands are needed. It should be pointed out that the excretion of a given drug by the normal and diseased gland can be different. Andrology, the science of the physiology and pathophysiology of the male genital organs, is in rapid development. Andrological pharmacology has recently been recognized as an important area. Previously it has been a neglected field in medicine. In some societies it is still very difficult—sometimes impossible—to obtain semen samples for analysis. The obstacles must be overcome. It must be a natural thing to take a semen sample for analysis. The split ejaculate technique can then be of considerable help. It is hoped that this survey will stimulate more active research in the field of andrological pharmacology.

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References


**Treatment of bacteraemia due to anaerobic bacteria**

Most of the literature on anaerobic bacteraemia, exclusive of that related to dental manipulation, has been published since 1967 (Finegold, 1977). Many reports have appeared in the ensuing years establishing the incidence of anaerobes in bacteraemia generally between 5 and 15% and, sporadically, as high as 25% (Wilson, Martin, Wilkowske & Washington, 1972). This variability in incidence is undoubtedly related to numerous factors, included among which are patient populations studied, likely portals of entry, prevalence of certain underlying diseases, frequency of intestinal and pelvic surgery, use of pre- or peri-operative antibiotic regimens, and blood culture techniques. The vast majority of clinically significant anaerobic bacteraemias are due to the Bacteroidaceae and, more specifically, *Bacteroides fragilis*; however, in approximately a third of instances these bacteraemias are polymicrobial (Wilson, Martin, Wilkowske & Washington, 1972), further complicating therapy and increasing mortality.

The morbidity and mortality associated with anaerobic bacteraemia should not be underestimated. Approximately one-third of the patients die, and the mortality rate rises to 44% in those with polymicrobial bacteraemia (Wilson, Martin, Wilkowske & Washington, 1972). Shock occurs commonly in clostridial septicemia; it also occurs in approximately one third of patients with anaerobic Gram-negative bacteraemia, an incidence that is somewhat lower than that (46%) reported by DuPont & Spink (1969) for all gram-negative septicemias in adults.

Most recent clinical studies of anaerobic bacteraemia have dealt with those due to the Bacteroidaceae, obviously reflecting their frequency relative to clinically significant anaerobic bacteraemias due to other genera. The ensuing discussion will, therefore, focus on bacteraemias due to this group of organisms.

Any analysis of the treatment of anaerobic bacteraemia is complicated by a number of variables. Studies by both Wilson, Martin, Wilkowske & Washington (1972) and Chow & Guze (1974) have clearly shown that shock was significantly correlated with mortality rate. Other factors specifically cited by Chow & Guze were (1) age and sex, with mortality occurring significantly more frequently in females and in patients over 40 years in age; (2) underlying disease, with mortality rates in patients with ultimately fatal underlying disease being significantly greater than in those with nonfatal underlying disease, using the categories of underlying disease described by McCabe & Jackson (1962); and (3) portal of entry. Mortality did not occur in any patients in whom the female genital tract was the portal of entry, in contrast to mortality rates of 50% in patients in whom the gastrointestinal and oropulmonary tracts were the portals of entry.

Chow & Guze (1974) examined the effect of