Leading articles

Non-specific vaginitis: its diagnosis and treatment

Many investigators agree (Gardner & Dukes, 1955; Akerlund & Mardh, 1974; Lewis et al., 1972; Pheifer et al., 1978) that non-specific vaginitis is often caused by an organism which has variously been named *Haemophilus vaginalis* (Gardner & Dukes, 1955) *Corynebacterium vaginale* (Zinneman & Turner, 1963) and *Gardnerella vaginalis* (Greenwood & Pickett, 1980). The taxonomic debate need not concern us further since the organism is able to be identified (Dunkelberg, 1977) in appropriate circumstances. It is important, though, to look at the practical diagnosis of the condition, the case for treatment and the choice of agent.

Non-specific vaginitis is common and benign (Gardner, 1980) so it would be inappropriate to suggest the use of specialized transport media and isolation techniques for diagnosis. Hence, the practical diagnosis will depend mainly on knowledge of the clinical picture, excluding other conditions as and when indicated by the history and physical examination.

The usual complaint is an offensive vaginal discharge which may cause little inconvenience to some patients. Others find the condition more distressing, particularly if the smell after sexual intercourse is pronounced and leads to comment from the partner. A minority have symptoms of local inflammation and then only in a mild form (Gardner & Dukes, 1955; Gardner, 1980). *H. vaginalis* is sexually transmitted but rarely causes symptoms in the male (Dunkelberg, 1977). It may cause urinary tract infections in the female (Lee & Schmale, 1973) but is rarely associated with serious infections. In these cases an underlying cause is usually apparent (Gardner, 1980) such as trauma, abortion or delivery.

The discharge is malodorous but less so than that of trichomoniasis. It is moderate in volume, typically grey and often there is minimal frothiness. The discharge tends to cling in a light film to the vaginal wall and it has the same thin homogeneous consistency as that seen in trichomoniasis. There may sometimes be minimal signs of vulvitis or vaginitis. Cervicitis may co-exist but it should be clearly understood that this is not caused by *H. vaginalis* (Gardner & Dukes, 1955) and non-specific cervicitis is an entirely different problem.

In the original description it was suggested that the withdrawn speculum be smelled to help distinguish the odour from that arising from the vulva (Gardner & Dukes, 1955) but the Amine test may be aesthetically more acceptable (Pheifer et al., 1978). This test consists of adding a drop of 10% KOH to a sample of discharge and noting the presence or absence of an amine-like odour best described as 'fishy'. Those who have used this method claim good correlation with culture results (Pheifer et al., 1978; Balsdon et al., 1980) but it remains to be seen whether all observers will be able to detect and recognize the smell, and it should be appreciated that the test will not exclude other infections.

Normal vaginal discharge is usually scanty, white and curdy but these are subjective criteria and it may be difficult, in practice, to adjust ideas of what constitutes normality without objective tests. The use of pH paper may be of help since the majority of infected discharges have a pH of 5·0 or above while normal secretions are more acid (Gardner & Dukes, 1955).

Looking for 'clue cells' in the infected discharge cannot be recommended as a routine. Those with a specialized interest and access to a microscope have not been able to place great reliance on this examination and the epithelial cell covered in organisms and seen on the wet film may turn out not to be covered in Gram-negative coccobacilli (true clue cell) but with a variety of organisms (Frampton & Lee, 1964).

The patient's symptoms are sufficient indication for treatment and the doctor will also be interested in preventing repeated consultations. A woman who does not receive effective treatment or does not think of asking for
it may cause herself further harm by her own attempts to cope with the problem. Excessive washing, douching, and use of vaginal deodorants are familiar enough but the practice of using tampons, sometimes perfumed, to control a discharge is perhaps not so widely recognized.

Treatment must be capable of use in either sex and be simple, efficient and free of significant side-effects. It should not induce thrush and ideally should have no activity against the gonococcus. The results of using local agents have not been good to date (Gardner, 1980) but in view of the mild nature of the condition further work is needed.

MIC measurements are an attempt to predict the clinical outcome from a knowledge of the in-vitro activity. In the case of H. vaginalis there have been some notable disparities in the results. The most promising drug identified in clinical practice, so far, has been metronidazole (Pheifer et al., 1978; Balsdon et al., 1980). H. vaginalis is unusual in that it is not a strict anaerobe, and it has been suggested that a combination of H. vaginalis and anaerobes are responsible for the clinical manifestations of the infection (Chen et al., 1979) and that anaerobes may protect other organisms from the body’s defence mechanisms (Ingham et al., 1977). However, metronidazole does have a significant effect in vitro, although disappointing in preliminary tests, has been shown to be influenced by time, inoculum size and whether strictly anaerobic conditions are used (Ralph, Austin, Pattison et al., 1979). It has also been suggested that vaginal concentrations may be more significant than blood levels (Balsdon, Taylor, Read et al., 1980).

In contrast, erythromycin is the most effective antibiotic so far identified in vitro (McCarthy, Mickelsen & Grover-Smith, 1979) but it performs poorly in the clinical situation. This has been attributed to a possible combination of pH effect with poor vaginal levels or inactivation by other bacteria (Durfee et al., 1979).

Gardner has recommended in order of efficiency, metronidazole, cephradine, cepalexin, ampicillin and tetracycline (Gardner, 1980) but others have found disappointing results with ampicillin and tetracycline (Pheifer et al., 1978; Balsdon et al., 1980). The agent of choice would appear to be metronidazole in a dose of 400–500 mg twice daily for 7 days (Pheifer et al., 1978; Balsdon et al., 1980) with treatment of the partner(s) simultaneously either at the initial diagnosis or in the event of relapse. The doubts about the safety of this drug would appear to have been dispelled at least for short term courses (Hartley, 1979). In the interest of conformity of prescribing, it will be interesting to discover if the 200 mg thrice daily 7-day course routinely prescribed for trichomoniasis and recommended for non-specific vaginitis (Robertson et al., 1980) proves to be as effective as the established regimens.

Jennifer Clay
Consultant Venerologist
Birmingham General Hospital
Steelhouse Lane
Birmingham B4 6NH, U.K.

References


**After pro-drugs—mutual pro-drugs**

A pro-drug is an inactive compound which is converted into active drug in the body. Pro-drugs are usually formulated to increase absorption or to decrease the risk of local side effects. There are many examples of pro-drugs in antimicrobial chemotherapy, the earliest being prontosil. This compound, studied by Domagk in 1935 was not active in *in-vitro* experiments, but was taken by mouth; it was, of course, because it is broken down in the body into the microbiologically active sulphanilamide. Usually antibiotic pro-drugs are esters, the ester or transport moiety increasing the lipophilicity of the molecule, aiding gastrointestinal absorption. The ubiquitous esterases of the body rapidly remove the ester moiety leaving the parent compound. The fate of the ester moiety has already been discussed in these columns (Bint, 1980). Bacampicillin, talampicillin and pivampicillin are all about twice as well absorbed as ampicillin, with twice the urine recovery so that lower daily dosages could be used. The esters of erythromycin also facilitate absorption. The succinate of chloramphenicol overcomes the problem of the bitter taste of the parent drug which makes it hardly palatable. The succinate is tasteless and is broken down into chloramphenicol either prior to or during absorption.

In the case of β-lactam antibiotics, the ester linkage utilizes the carboxylic acid grouping at the 3-position. This has raised the novel and interesting possibility of producing ‘mutual pro-drugs’. These are derived from the combination of two compounds through this ester link so that each in effect acts as the pro-drug for the other. An earlier such compound was an amoxicillin/probenecid mutual pro-drug (Christensen & Leanza, 1976), the aim being to prolong the effect of the amoxicillin. After the finding that mecillinam and ampicillin showed modest synergy (Lund et al., 1976) a mutual pro-drug of this combination, linked via their respective 3-carboxy groups, was described (Grünberg & Cleeland, 1977).

Neither of these two compounds have been tried clinically.

To my mind, a far more exciting development has emerged from the problems associated with β-lactamase inhibitors. Here the aim is to deliver to the body both inhibitor and antibiotic.

In a patent application filed by von Daehne & Godtfredsen (1980) this aim is claimed to have been achieved with the synthesis of linked esters of penicillins and β-lactamase inhibitors, such as penicillanic acid sulphone (CP-45,899; sulbactam), β-halopenicillanic acids or clavulanic acid. Two such compounds, the linked esters of penicillanic acid sulphone with ampicillin and mecillinam, are described in more detail in a paper from the same group (Baltzer et al., 1980). Absorption of both ampicillin and mecillinam is enhanced above that expected from either compound administered alone and the levels of the penicillanic acid sulphone are similar to the two former compounds. Absorption of the mutual pro-drugs appears to be complete and hydrolysis to the two constituents rapid.

It is possible that the gastrointestinal side effects of the β-lactamase inhibitors is related to incomplete absorption (there may though be other reasons). The use of the mutual pro-drugs may avoid this problem.

**Mutual pro-drugs** are a novel development, but certain ground rules are apparent (Baltzer et al., 1980). It goes without saying that the mutual pro-drug must be well absorbed and the two active constituents released equally. The distribution and elimination of the two constituents should ideally be similar in health and disease. Of greatest importance, the two constituents should