Cancer Chemother Pharmacol (1982) 9:118–119

Cancer Chemotherapy and Pharmacology

Short Communication

Absorption and Distribution of Vaginally Administered Misonidazole

Daniel Ash[1], Roland Bugden[2], and Robert Calvert[3]

[1] Cookridge Hospital, Leeds 16
[2] Institute of Cancer Research, Downs Road, Sutton, Surrey
[3] Leeds General Infirmary, Leeds 1, Great Britain

Introduction

The radio-sensitiser misonidazole has been shown in numerous animal studies to be an effective sensitiser of hypoxic cells [4], but its use in man is restricted by the development of peripheral neuropathy, which is its dose-limiting toxicity after oral administration. It would be an advantage therefore if high levels of the drug could be delivered directly to the tissues to be treated without incurring systemic toxicity. This has been shown to be possible in previous studies where misonidazole was instilled into the bladder [3], and it has therefore been investigated for its potential use in cancer of the cervix, where misonidazole can be delivered to the vaginal vault relatively simply, and if necessary repeatedly.

Patients and Methods

Two groups of patients were studied. In nine cases misonidazole was administered vaginally before hysterectomy for benign disease. For the first four cases 1 g misonidazole was given as a solution in 25 ml water absorbed into a cotton wool tampon which was placed at the vaginal vault 3–4 h before operation. In the other five patients 1 g misonidazole was given in a pessary which was inserted 12–14 h before surgery. For all patients a sample of blood was taken at the time of operation and tissue samples taken from vaginal mucosa, ecto-cervix, endo-cervix, endometrium, proximal parametrium, and myometrium at intervals from the cervix (see Fig. 1). All samples were frozen in liquid nitrogen before analysis by high-performance liquid chromatography (HPLC) [5], and informed consent was obtained from all patients.

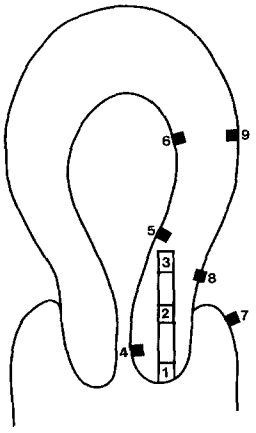

Fig. 1. Diagram to show site of tissue samples from the uterus

Reprint requests should be addressed to D. Ash

The systemic absorption and excretion of vaginally administered misonidazole was studied in eight patients who were receiving intracavitary cathetron radiation for cancer of the cervix. At the end of treatment, while the patients were still under anaesthetic, 1 g misonidazole was inserted into the vaginal vault either in solution (5 patients) or by pessary (3 patients). Serial samples of blood and urine were then taken at intervals over the next 24 h to assess the absorption and excretion of the drug.

Results

The results show that systemic absorption of misonidazole from the vagina was slower and less complete than that demonstrated in studies with administration PO [2]. Peak blood levels were achieved 8–10 h after administration and the half-life varied from 9.5 to 21.25 h. The average peak blood level was 8.8 μg/ml, compared with an average of 21.7 μg/ml after an oral dose of 1 g [2]. There was no significant difference between patients according to whether they had received misonidazole in solution or as a pessary.

Serial measurements of urinary excretion showed that the total amount of drug excreted in the first 24 h after vaginal administration varied from 2% to 5% of the dose. Similar studies following oral administration show that 10%–20% of the dose can be detected in the urine [1].

The results of the tissue levels, expressed as total nitroimidazole, are shown in Table 1. These indicate that 3–4 h after application the amount of drug near the absorbing surface is higher than after 12–14 h, but that there is little difference in tissue levels deeper within the uterus. It was noted, however, that the proportion of drug measured as the *O*-demethylated metabolite desmethyl misonidazole was 40%–50% in the tissue samples taken 12–14 h after administration but less than 2% in the samples taken at 3–4 h.

Within 5 mm of the surface epithelium drug levels fell by 50%–75%, and similar falls were noted for both short and long exposure times. Not surprisingly, however, blood levels were higher 3–4 h after dosing than at 12–14 h. For patients given misonidazole 12–14 h before assay there was a tissue-to-blood ratio of approximately 3 to 1, compared with 1 to 3 for patients who had received the drug 3–4 h before assay.

0344-5704/82/0009/0118/$ 01.00

Table 1. Nitroimidazole levels in tissue samples taken from the positions shown on Fig. 1

Site of tissue sample	Mean tissue level of nitroimidazole (μg/mg) ± SD	
	3 – 4 h $n = 3$	12 –14 h $n = 5$
Blood	14.5 ± 5.2	2.9 ± 1.75
1	33.6 ± 30.6	13.7 ± 6.7
2	5.4 ± 1.7	6.6 ± 1.5
3	5.0 ± 2.7	5.4 ± 2.2
4	10.4	11.3 ± 2.7
5	4.3	8.9 ± 4.5
6	5.4	8.0 ± 2.8
7	32.5 ± 17.1	21.6 ± 12.8
8	12.6 ± 6.0	12.4 ± 5.8
9	7.4 ± 2.5	12.3 ± 6.9

Discussion

In spite of the fact that a tissue-to-blood ratio of 3 to 1 was obtained by giving misonidazole vaginally, the tissue levels achieved were insufficient to produce any predictable degree of radio-sensitisation, and were less than can be achieved after oral administration of the same dose. After 1 g misonidazole PO an average tissue level of 19.3 μg/g was achieved in the cervix [2], compared with 8.2 μg/g for non-surface tissue after intravaginal application.

The results in eight of the nine patients were fairly consistent and suggest that there is little advantage to be gained by giving misonidazole in this way. In one other case however, which was excluded from the analysis, a tissue level of 410 μg/g was measured at the ecto-cervix, and 64.2 μg/g in the proximal parametrium. This might perhaps be due to optimum positioning of the drug in the vaginal vault, but unless such positioning can be guaranteed and regularly reproduced, it cannot be relied upon for clinical use.

The results overall suggest that misonidazole diffuses poorly into the cervix and uterus following vaginal administration and that systemic absorption is incomplete and delayed compared with oral dosing. The local tissue concentration might be increased by employing doses larger than 1 g, and a different vehicle and technique for applying misonidazole vaginally may perhaps also improve results, but the results of the present study suggest that this approach is unlikely to be helpful in the management of patients with cancer of the cervix.

Acknowledgement. The co-operation of Mr K. Hancock, Senior Lecturer in Obstetrics and Gynaecology, The Hospital for Women, Leeds, is gratefully acknowledged.

References

1. Ash DV, Smith MR (1979) Biliary and faecal excretion of misonidazole in man. Br J Radiol 52: 846–848
2. Ash DV, Smith MR, Bugden RD (1979) Distribution of misonidazole in human tumours and normal tissues. Br J Cancer 39: 503
3. Awwad HK, El-Merbzabani MM, Burgers MV (1978) Penetration of misonidazole after intravesical administration in cases of carcinoma of the bilharzial bladder. Br J Cancer 37: [Suppl III] 297–298
4. Denekamp J, Fowler JF (1978) Radiosensitisation of solid tumours by nitro-imidazoles. Int J Radiat Oncol Biol Phys 4: 143
5. Workman P, Little CJ, Marten TR, Flockhart IR, Bleehen NM (1978) Estimation of the hypoxic cell sensitiser misonidazole and its *O*-demethylated metabolite in biological material by reversed phase high-performance liquid chromatography. J Chromatogr 145: 507–512

Received May 6, 1982/Accepted August 2, 1982