

erg) tydens 10 dae na onttrekking van die middels geëvalueer. Die eindevaluasie was die meting wat op die hoogste getal dae gemaak is, met ander woorde op 5 of meer dae. Die tydsverloop vanaf die staking van inname van die middels tot die eerste ontstaan van hierdie onttrekkingsimptome is ook waargeneem.

Gevolgtrekking en bespreking

Ses van die 15 pasiënte wat met oksasepam behandel was, het wel onttrekkingsimptome getoon, terwyl slegs 2 van die 15 pasiënte wat met chloordiasepoksied behandel was, onttrekkingsimptome getoon het. Die hoër insidensie van onttrekkingsimptome met die kortwerkende bensodiasepiene in vergelyking met die langwerkendes was opvallend, maar is nie statisties betekenisvol nie. Die onttrekkingsimptome as gevolg van die gebruik van die kortwerkende middel het gouer na staking van die middel voorgekom. Hierdie verskil is statisties betekenisvol.

Die kortwerkende bensodiasepiene het nie aktiewe metaboliëte nie, en daar is nie 'n geleidelike afname van

hul farmakologiese en kliniese effekte nie.^{3,4} Die weinig tyd vir farmakodinamiese en farmakokinetiese aanpassing na skielike staking van gebruik van die middels verklaar moontlik die opvallende hoë insidensie van onttrekkingsimptome. Hierdie oënskynlike nadeel van langtermyn-toediening van die kortwerkende middels kan waarskynlik voorkom word deur die dosering geleidelik oor 'n aantal dae te verminder.

Sommige alkoholiste is fisies afhanklik van beide alkohol en die bensodiasepiene.⁵ Indien die bensodiasepiene en alkohol gelyktydig by sulke pasiënte onttrek word, kan die alkohol-onttrekkingsindroom vererger word.

VERWYSINGS

1. Marks, J. (1978): *The Benzodiazepines: Use, Overuse, Misuse, Abuse*. 1ste uitg., bl. 80. Lancaster: MTP.
2. Mandelli, M., Tognoni, G. en Garratini, S. (1978): *Clin. Pharmacokin.*, 3, 72.
3. Kramp, P. (1978): *Acta psychiat. scand.*, 58, 1974.
4. Sellers, E. M. en Kalant, H. (1976): *New Engl. J. Med.*, 294, 757.
5. Hosein, I. N. (1978): *Curr. med. Res.*, 5, 632.

Combination of radiosensitizers and hyperthermia in tumour radiotherapy

V. BRÜCKNER

Summary

Specific metabolic properties of hypoxic (and therefore radio-resistant) tumour cells are responsible for the selective effect of radiosensitizers (such as misonidazole) and hyperthermia upon these cells in respect of radiosensitization as well as cytotoxicity. Radiosensitizers and hyperthermia should therefore be used to improve the results of tumour radiotherapy; enhancement ratios of 2-4 have already been attained experimentally with this combined treatment. In spite of these good results, certain problems exist, and up to now the combination of radiosensitizers and hyperthermia has not been used to any great extent for tumours in humans.

S. Afr. med. J., 59, 116 (1981).

Hypoxic tumour cells are a major problem in radiotherapy since they are only slightly radiosensitive and therefore very often the starting point of tumour recurrence.^{1,11} The percentage of hypoxic cells in a tumour depends on its age; for experimental tumours, values of up to 50% are cited.^{1,11} For a long time attempts have been made to overcome this difficulty by bringing about a general increase in tumour radiosensitivity. Two promising methods are the use of chemical radiosensitizers (especially misonidazole) shortly

before irradiation,^{7,11} and induction of local hyperthermia immediately before or during or immediately after irradiation.^{6,8,10,11,16,22,23}

The metabolic difference between normal and tumour cells (Fig. 1) is due to the fact that in cancer cells, and especially in hypoxic cancer cells, fermentation plays a greater role than in normal cells.^{4,24,25} Because of the related lactic acid production, tumour cells in general and especially hypoxic tumour cells have a lower pH value than normal cells.^{4,24,25} Radiosensitizers and hyperthermia exercise not only a radiosensitizing effect but also a cytotoxic effect (Fig. 2). The radiosensitizing effect affects hypoxic cells exclusively.^{2,3} As regards the cytotoxic effect of the radiosensitizers^{5,12,21} as well as the radiosensitizing^{14,28} and cytotoxic effects^{11,15-17,27} of hyperthermia, it was found experimentally and quite astonishingly that hypoxic cells are always more sensitive than normoxic cells. This means that radiosensitizers as well as hyperthermia act selectively upon hypoxic cells; one reason for this may be their lowered pH value.^{6,11,17,25} Hence not only can radiosensitizers and hyperthermia be used alone but they can also be combined in radiotherapy in order to increase the desired effects.

Table I shows early results. The enhancement ratio is the relationship between a radiation dose for a certain biological effect and that radiation dose which, with simultaneous administration of misonidazole and/or hyperthermia, leads to the same effect. The therapeutic value of the method is thus in direct proportion to the enhancement ratio, and the combination of a radiosensitizer such as misonidazole and hyperthermia is always more effective than either method used alone. Misonidazole and hyperthermia are also effective under neutron irradiation. With misonidazole and hyperthermia, enhancement ratios of 2-4 have been attained.

Departments of Medical Physics and Radiology, Tygerberg Hospital and University of Stellenbosch, Parowvallei, CP

V. BRÜCKNER, DIPL. PHYS., DR. RER. NAT. (Present address: Radiological University Clinic, Arnold-Heller Street 9, Kiel, West Germany)

Date received: 22 January 1980.

Despite these good experimental results, this combined treatment has not so far been extensively used for tumours in human subjects. Possible reasons for this are: (i) technical difficulties in administering local hyperthermia (especially with deep-lying tumours); (ii) the risk of polyneuropathy with misonidazole, which has limited the dose to 80 mg/kg per fraction with a total not more than approximately 30 g.^{9,13} In contrast, in mice 500 - 1 000 mg/kg have been administered,^{18-20,28} resulting in greater radiosensitization; (iii) the effect of hyperthermia in increasing the cytotoxicity of misonidazole and at the same time reducing its selectivity for hypoxic cells;¹² (iv) the effect of misonidazole on temperature regulation;¹⁸ combined treatment could be either advantageous (raising body temperature)¹⁸ or disadvantageous (lowering body temperature);²⁸ this would in either case make it more difficult to produce optimal results. It is hoped that these difficulties will soon be overcome, for instance through the development of more suitable hyperthermia apparatus or techniques, or the synthesis of better radiosensitizers.

REFERENCES

1. Alper, T. (1973): Brit. med. Bull., 29, 3.
2. Asquith, J. C., Foster, J. L., Willson, R. L. et al. (1974): Brit. J. Radiol., 47, 474.
3. Asquith, J. C., Watts, M. E., Patel, K. et al. (1974): Radiat. Res., 60, 108.

4. Bauer, K. H. (1963): *Das Krebsproblem*, 2nd ed. Berlin: Springer-Verlag.
5. Bleehen, N. M., Honess, D. J. and Morgan, J. E. in Streffer, C., Van Beuningen, D., Dietzel, F. et al., eds (1978): *Cancer Therapy by Hyperthermia and Radiation*, p. 62. Baltimore: Urban & Schwarzenberg.
6. Brückner, V., Zywiets, F. and Jung, H. (1979): *Strahlentherapie*, 155, 44.
7. Brückner, V. (1979): *S. Afr. med. J.*, 56, 528.
8. Dietzel, F., Linhart, G. and Fleischhauer, B. (1979): *Strahlentherapie*, 155, 126.
9. Dische, S., Gray, A. J. and Zanelli, G. D. (1976): *Clin. Radiol.*, 27, 159.
10. Field, S. B. and Bleehen, N. M. (1979): *Cancer Treatment Reviews*, 6, 63.
11. Hall, E. J. (1978): *Radiobiology for the Radiologist*, 2nd ed., Hagerstown, Md: Harper & Row.
12. Hofer, K. G. in Streffer, C., Van Beuningen, D., Dietzel, F. et al., eds (1978): *Op. cit.*,⁵ p. 264.
13. Jentsch, K., Kärcher, K. H., Kogelnik, H. D. et al. (1977): *Strahlentherapie*, 153, 825.
14. Kim, S. H., Kim, J. H. and Hahn, E. W. (1975): *Radiology*, 114, 727.
15. *Idem* (1975): *Brit. J. Radiol.*, 48, 872.
16. Leith, J. T., Miller, R. C., Gerner, E. W. et al. (1977): *Cancer*, 39, 766.
17. Overgaard, J. and Bichel, P. (1977): *Radiology*, 123, 511.
18. Overgaard, J. (1979): *Brit. J. Cancer*, 39, 96.
19. Porschen, W., Gartzten, J., Gewehr, K. et al. (1978): *Ibid.*, 37, suppl. III, p. 194.
20. Porschen, W., Weber, H. J., Mühlensiepen, H. et al. (1978): *Brit. J. Radiol.*, 51, 937.
21. Stratford, I. J., Watts, M. E. and Adams, G. E. in Streffer, C., Van Beuningen, D., Dietzel, F. et al., eds (1978): *Op. cit.*,⁵ p. 267.
22. Streffer, C., Van Beuningen, D., Dietzel, F. et al., eds (1978): *Op. cit.*,⁵
23. Streffer, C. and Van Beuningen, D. (1979): *Medizin in unserer Zeit*, 3, 50.
24. Von Ardenne, M. (1970): *Klin. Wschr.*, 48, 1397.
25. *Idem* (1979): *Medizin in unserer Zeit*, 3, 34.
26. Von Burg, R., Conroy, P. J. and Passalacqua, W. (1979): *Brit. J. Cancer*, 40, 134.
27. Weber, H. J., Porschen, W. and Feinendegen, L. E. (1978): *Brit. J. Radiol.*, 51, 937.

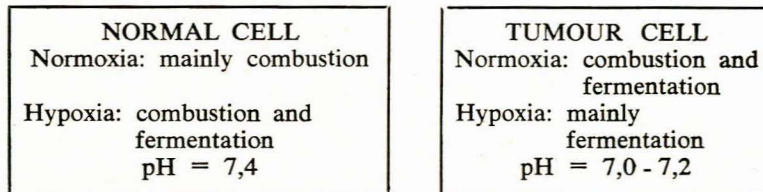
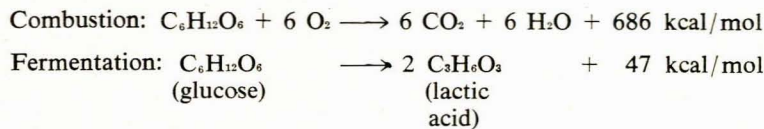


Fig. 1. Metabolic difference between normal and tumour cells.

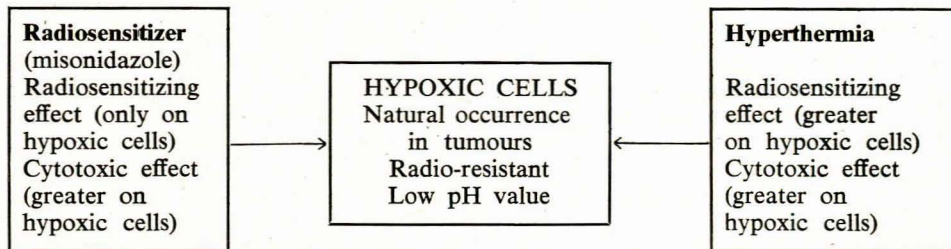


Fig. 2. Selective effects of radiosensitizers and hyperthermia on hypoxic cells.

TABLE I. ENHANCEMENT RATIOS ATTAINED

Model and criterion	Hofer ¹²	Porschen et al. ^{19,20} Weber et al. ²⁷	Porschen et al. ^{19,20}
	Hypoxic mouse tumour cells <i>in vitro</i> - <i>in vivo</i> (survival) X-irradiation	Mouse tumour <i>in vivo</i> (cell loss rate, regression, growth delay, TCD _{50/100}) ⁶⁰ Co-gamma irradiation	Mouse tumour <i>in vivo</i> (cell loss rate, regression, growth delay, TCD _{50/100}) Neutron irradiation (E = 6 MeV)
Misonidazole plus irradiation	2,1 (1 mg/ml)	1,5 (500 mg/kg)	1,1 - 1,3 (500 mg/kg)
Irradiation plus hyperthermia	1,9 (60 min at 41,5°C)	2,8 (60 min at 42°C, locally)	2,2 (60 min at 42°C, locally)
Misonidazole plus irradiation plus hyperthermia	4,3	3,1	2,4

TCD_{50/100} = tumour cure dose, i.e. radiation dose which cures/controls 50% of the treated tumours within 100 days.