International Journal of Pharmaceutics, 76 (1991) 187–190

ADONIS 037851739100347Z

IJP 02557

Photochemical interaction between triamterene and hydrochlorthiazide

Douglas E. Moore and Julia L. Mallesch

Department of Pharmacy, The University of Sydney, Sydney 2006 (Australia)

(Received 15 March 1991)
(Modified version received 7 June 1991)
(Accepted 20 June 1991)

Key words: Photooxidation; Flash photolysis; Photodegradation; Photochemical interaction; Photochemistry; Diuretic drug

Summary

Flash photolysis and steady-state photosensitized oxidation experiments have been used to show that there is an interaction or cross-sensitization between the diuretic drugs, triamterene and hydrochlorthiazide, when irradiated with UV light in the same solution. The size of the effect observed was not sufficient to conclude that a combination diuretic formulation of hydrochlorthiazide and triamterene would be markedly less stable to the effects of UV light compared to the individual drugs, nor to suggest that it could lead to a greatly increased incidence of adverse phototoxic responses for the combination diuretic formulation.

Within the diuretic class of drugs, many (e.g., chlorthiazide, hydrochlorthiazide and frusemide) have been associated with adverse photosensitivity responses, observed as an exaggerated sunburn-like reaction to sunlight (Magnus, 1976).

Preparations are available which utilize hydrochlorthiazide (HCT) individually or in a combined formulation with triamterene (TRT) or amiloride (AML), designed to decrease the severity of the potassium loss in diuresis.

From the reports to the Australian Adverse Drug Reactions Advisory Committee (ADRAC, 1987), the incidence of photosensitivity for the combination formulations is apparently greater than that for the diuretic agents in individual use. There are many limitations to this information, such as the widely recognised biases common to all voluntary reporting systems for monitoring drug safety.

Both HCT and TRT have heterocyclic structures which absorb light in the UV region, making them potential sensitisers. The photochemistry of HCT has been investigated previously in terms of photosensitized oxidation, free radical polymerization and photodegradation studies. It has been shown for HCT and for other related compounds that the chlorine substituent on the aromatic ring is photolabile, and that its loss is the source of free radical activity (Tamat and Moore, 1983). Photochemical studies have not been performed previously on TRT, even though photosensitivity responses have been recorded (Martindale, 1989). Since there is an overlap of the UV absorption and fluorescence spectra of

Correspondence: D.E. Moore, Dept of Pharmacy, The University of Sydney, Sydney 2006, Australia.

the two compounds, the question arises as to whether an interaction could occur between HCT and TRT to generate a photobiological response for the combination greater than for the individual drugs. A study has therefore been carried out, using both steady-state and transient irradiation, to investigate the possibility of an interaction between the two drugs ensuing from UV light absorption.

Spectroscopic properties: The chemical structures of HCT and TRT, and their absorption spectra at a concentration of 10^{-5} M in pH 7.0 phosphate buffer are shown for the relevant UVA and UVB ranges (280–400 nm) in Fig. 1. Each compound displays a small bathochromic shift with increasing pH as the ionization state changes. HCT has two ionization equilibria with pK_a values of 8.6 and 9.9 (Deppler, 1981), while that of TRT is 6.2 (Martindale, 1989). HCT has a weak fluorescence emission at 370 nm, but TRT emits very strongly at 436 nm with approx. 100-fold greater quantum efficiency. The excitation wavelength for TRT is very close to the emission wavelength of HCT; potentially, energy transfer could occur from HCT to TRT. However, due to the very strong fluorescence of TRT, and the weak fluorescence of HCT, fluorescence measurements were not able to detect changes in the emission characteristics of TRT in the presence of HCT.

Flash photolysis: Laser flash photolysis (using 355 nm excitation) was performed as previously described (Moore and Chappuis, 1988) on a nitrogen-gassed solution of TRT (1.7×10^{-5} M in 0.05 M phosphate buffer pH 7.0). The nature of each transient species was deduced by observing the decay kinetics in the presence of suitable scavengers (Bensasson et al., 1983). The solvated electron was indicated by its characteristic broad absorption maximum around 700 nm. Bubbling of the solution with nitrous oxide (an electron scavenger) during photolysis led to the disappearance of both the electron signal at 700 nm and the concomitant absorption at 440 nm. Bubbling with oxygen did not affect the decay of the 440 nm absorption, suggesting that it was due to a cationic species formed from TRT and not a triplet state. Thus, photoionization appears to be the primary photochemical event for TRT.

HCT does not absorb sufficiently at 355 nm to enable flash photolysis at that wavelength. When 266 nm excitation was used for HCT, a small

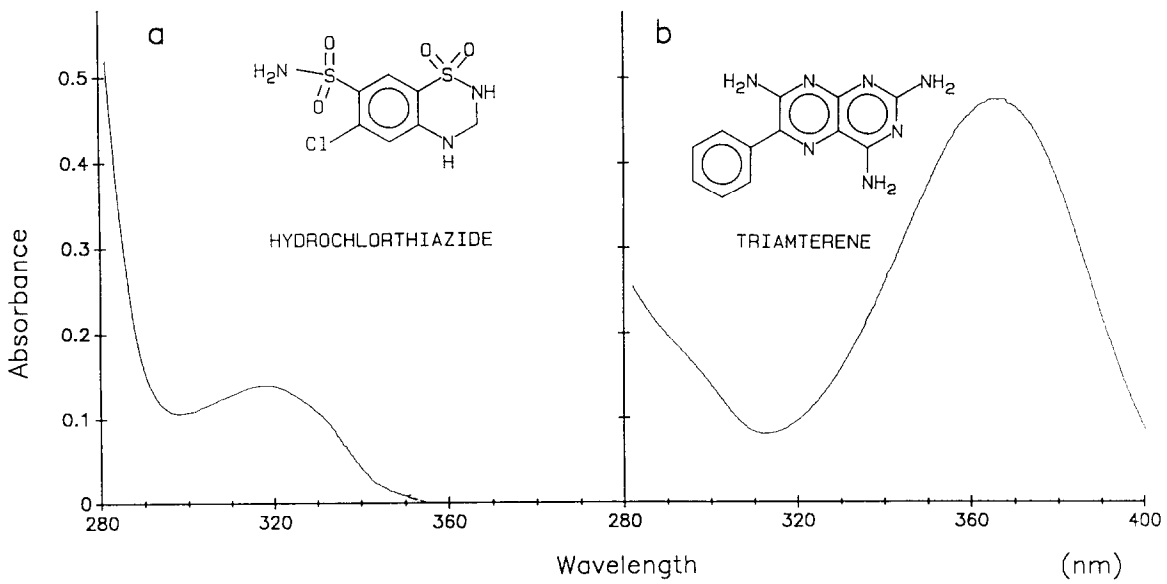

Fig. 1. Ultraviolet absorption spectra for the region 280–400 nm of solutions of (a) hydrochlorthiazide and (b) triamterene, each at a concentration of 10^{-5} M in pH 7.0 buffer.

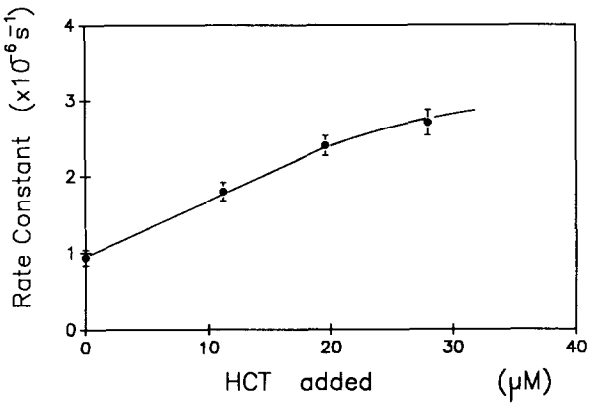

Fig. 2. Effect of added hydrochlorthiazide on the rate constant for the decay of the transient absorption at 700 nm obtained in laser flash photolysis at 355 nm of triamterene (1.7×10^{-5} M in pH 7.0 buffer).

broad absorption was observed between 350 and 450 nm, with no evidence of solvated electron at 700 nm. From these observations, it was concluded that a sample of TRT with HCT added could be examined with 355 nm laser excitation such that no resulting absorption would be ascribable to HCT alone.

A series of solutions containing 1.7×10^{-5} M TRT with added HCT in the concentration range up to 2.8×10^{-5} M were studied. The significant effect of HCT on TRT was seen as an acceleration of the rate of decay of the solvated electron absorption at 700 nm. This increase in the rate of decay was proportional to the amount of HCT added, as shown in Fig. 2. Thus, ground-state HCT appears to scavenge the electron formed on photoionization of TRT. This effect might be expected to result in an increased rate of decomposition of HCT.

Photodegradation: HPLC analysis was used to determine the degradation profile of TRT and HCT when irradiated together under anaerobic conditions, at both pH 7.0 and 11.0. Separation of HCT and TRT from their photoproducts was achieved using a Brownlee RP-MP (5 μm) C18 cartridge column (100×4.6 mm) and mobile phase consisting of 0.04 M phosphate buffer (pH 7.8), acetonitrile and methanol (78:17:5).

The photodegradation of TRT proceeded very slowly in comparison to that of HCT, even though the irradiating source has its maximum output at 365 nm where TRT absorbs maximally.

Analysis of TRT photolysis in the presence of HCT indicated that the rate of photodegradation of TRT is essentially unaffected by the HCT. There was a slight acceleration in TRT degradation at long irradiation times, at which stage most of the HCT had degraded. On the shorter time scale, however, the HCT degradation was slightly reduced. There was no significant difference between the rates at pH 7.0 and 11.0.

Photooxidation: As a guide to the ability of a photosensitizer to generate the active oxygen species, singlet molecular oxygen, by energy transfer from the triplet state, the oxygen uptake by a singlet oxygen specific substrate, such as histidine, can be studied (Moore and Hemmens, 1982).

In the absence of the sensitiser, oxygen uptake on irradiation was less than 0.2 μM min^{-1}. The oxygen uptake rates photosensitized by HCT and TRT when mixed together in the same solution were compared to the sum of the individual rates obtained when the two drugs were examined separately at the same concentration, with the results shown in Fig. 3. The significant increase in the histidine oxygen uptake rate in the combined solution suggests that there is some interaction

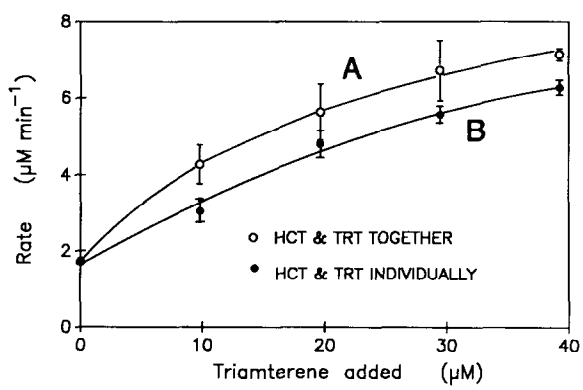

Fig. 3. Rate of oxygen uptake by histidine photosensitized by hydrochlorthiazide and triamterene at pH 7.0 and 30°C. Curve A was obtained from solutions containing both 1×10^{-5} M hydrochlorthiazide and varying amounts of triamterene. Curve B was calculated by summation of the rates obtained from individual solutions containing 1×10^{-5} M hydrochlorthiazide and the corresponding amounts of triamterene.

between HCT and TRT following irradiation, manifested by a faster rate of oxygen uptake.

Overall, the results of the transient and steady-state experiments conducted in this study show that there is only a minor interaction or cross-sensitization between HCT and TRT when irradiated with UV light in the same solution. The size of the effect observed is not sufficient to suggest that the combination formulations might be markedly less stable to the effects of UV light compared to the individual drugs. Equally, one could not support its implication as a substantial factor in the apparently increased incidence of phototoxicity reported for the combination diuretic formulation. Nonetheless, both HCT and TRT are photoactive drugs, and due caution should be exercised in relation to their use combined with exposure to sunlight.

Acknowledgements

The flash photolysis experiments were performed at The Center for Fast Kinetics Research at The University of Texas at Austin. C.F.K.R. is funded jointly by the Biotechnology Branch of the Division of Research Resources of NIH (RR00886) and by the University of Texas at Austin. The assistance of Dr S.J. Atherton is gratefully acknowledged. This work was partially funded by The Australian Research Council Small Grants Scheme.

References

Adverse Drug Reactions Advisory Committee, A sunburnt country revisited. *Adverse Drug Reactions Bulletin*, February, 1987 (Australian Dept of Health, Canberra).

Bensasson, R.V., Land, E.J. and Truscott, T.G., *Flash Photolysis and Pulse Radiolysis*, Pergamon, Oxford, 1983, pp. 8–11.

Deppler, H.P., Hydrochlorothiazide. *Anal. Profiles Drug Subst.*, 10 (1981) 405–441.

Magnus, I.A., *Dermatological Photobiology*, Blackwell, London, 1976, pp. 211–235.

Martindale, *The Extra Pharmacopoeia*, 29th Edn, 1979, Reynolds, J.E.F. (Ed.), The Pharmaceutical Press, London, p. 991, 1003.

Moore, D.E. and Chappuis P.P., A comparative study of the photochemistry of the non-steroidal anti-inflammatory drugs, naproxen, benoxaprofen and indomethacin. *Photochem. Photobiol.*, 47 (1988) 173–181.

Moore, D.E. and Hemmens, V.J., Photosensitization by antimalarial drugs. *Photochem. Photobiol.*, 36 (1982) 71–77.

Tamat, S.R. and Moore, D.E., Photolytic decomposition of hydrochlorthiazide. *J. Pharm. Sci.*, 72 (1983) 180–183.