J. Pharm. Pharmacol. 1990, 42: 502–504
Communicated November 9, 1989

The interaction of orally administered iron with levodopa and methyldopa therapy

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Abstract—The ability of methyldopa and levodopa to interact with both ferrous and ferric iron under a variety of conditions likely to be encountered physiologically has been examined. Spectrophotometric studies of ferrous sulphate in the presence of methyldopa indicate that no complexation occurs below pH 2, whilst between pH 4–9, a variety of iron-methyldopa complexes is formed. The formation of these complexes is fast at high pH (pH 9: $t_{\frac{1}{2}} < 5$ s), whilst the rate slows as the pH is lowered (pH 4: $t_{\frac{1}{2}} > 30$ min). These complexes are characteristic of iron-catecholate species, indicating that in the presence of methyldopa (and levodopa) ferrous iron undergoes autoxidation to the ferric form. The tight binding of ferric iron to methyldopa is predicted to alter the biodistribution characteristics of the complex with respect to the unchelated components. Furthermore, under the acid conditions of the stomach, redox cycling can occur. This will result in both catechol oxidation and production of the toxic hydroxyl radical. The findings suggest that care should be exercised when simultaneous administration of either methyldopa or levodopa with ferrous sulphate is indicated.

Recently, it has been reported that the concurrent oral administration of ferrous salts substantially alters the rate of both methyldopa (Campbell et al 1988) and levodopa (Campbell & Hasinoff 1989) absorption. The metabolism of methyldopa in chronic hypertensive patients on long-term methyldopa is also affected. These interactions lead to significant rises in blood pressure with methyldopa and may be associated with inadequate therapy with levodopa. Both methyldopa (**1a**) and levodopa (**1b**) contain a catechol function and will consequently bind ferric iron tightly, but not ferrous iron (Scheme 1) (Hider et al 1981). As pointed out (Campbell & Hasinoff 1989), under aerobic conditions, ferrous iron undergoes autoxidation to ferric iron in the presence of strong chelating agents such as catechol-containing moieties (eqn i) (Hider et al 1981). This reaction is strongly favoured in the pH range 4–9. However, under acid conditions (pH 2–5), ferric iron undergoes an internal redox reaction with catechol, which regenerates the ferrous ion (eqn iii) (Mentasti & Pelizzetti 1973; Hider et al 1981). Thus, in principle, a redox cycle can be set up, with the net effect being the oxidation of the catechol moiety by oxygen, as indicated in eqn iv. Operation of such a redox cycle (Scheme 2) has two implications: (i) considerable amounts of superoxide anion will be produced, which in the presence of ferrous iron is rapidly converted to the extremely toxic hydroxyl radical (Halliwell 1988); and (ii) many catechol-containing molecules can be oxidized by a single iron atom. If this redox cycling occurs in-vivo, then not only will the bioavailability of catechol-containing pharmaceuticals be reduced by complex formation, but also by iron-catalysed oxidation.

In this study, we investigated the possibility of both the autoxidation of ferrous iron and the acid reduced reduction of ferric iron in the presence of methyldopa and levodopa.

Methods

A series of experiments investigating the binding of iron by methyldopa were performed. The formation of the various iron complexes was monitored by UV/visible spectroscopy using a Perkin-Elmer Lambda 5 spectrophotometer (Perkin-Elmer, Cambridge, UK). Spectra were recorded in 1 cm pathlength cells, at a temperature of 37·0 (±0·1)°C. A variety of buffer systems, with minimal metal ion chelating ability wherever possible, was used, namely: acetate (50 mM; pH 4·0, 5·0); MES (2-[*N*-morpholino]ethanesulphonic acid; 50 mM; pH 6·0); MOPS (3-[*N*-morpholino]propanesulphonic acid; 50 mM; pH 7·0), HEPES (*N*-[2-hydroxyethyl]piperazine-*N*-[2-ethanesulphonic acid]; 50 mM; pH 8·0) and CHES (2-[*N*-cyclohexylamino]ethanesulphonic acid; 50 mM; pH 9·0). Methyldopa and levodopa were obtained from Sigma Chemical Co., Poole, UK. Ferric iron (as an atomic absorption standard solution in 2% nitric acid), and ferrous sulphate, heptahydrate (ACS reagent) were obtained from Aldrich Chemical Co., Gillingham, UK. All were used without further purification.

For comparative purposes, the UV/visible spectra of various iron (III) complexes of methyldopa were recorded. The complexes were prepared at three pH values (4·0, 7·0 and 9·0), by the addition of ferric nitrate to methyldopa (final concentrations: iron, 1 mM; methyldopa, 6 mM). The corresponding iron (II) methyldopa complexes were prepared in an analogous manner, by addition of ferrous sulphate to methyldopa (final concentrations 1 and 6 mM, respectively, as before). In all cases, spectra were recorded at 1 min intervals until complex formation was complete, as evidenced by no further increase in absorbance.

Results

Methyldopa (**1a**) has been shown to bind ferric iron over the pH range 4·0–9·0 (Fig. 1). The visible spectrum at pH 9·0 corresponds to the 3:1 complex (**3**). The spectrum at pH 7·0 is indicative of the presence of a mixture of two iron complexes; the 2:1 complex (**2**) and the 3:1 compound (**3**). This behaviour is typical of bidentate catechols (Hider et al 1981). At pH 4·0, a green complex is formed between methyldopa and iron (Fig. 1). This is the 1:1 complex, which undergoes an internal redox reaction, to form the semiquinone and ferrous iron (Mentasti & Pelizzetti 1973; Hider et al 1981) (eqn iii). The resulting semiquinone undergoes disproportionation to the quinone (**5**) and the parent catechol (eqn iv). Thus, depending on the pH of the solution, a wide range of iron-methyldopa complexes exists. A similar range of spectra was obtained for levodopa and iron (data not shown).

When ferrous iron (1 mM) was added to either methyldopa or levodopa (6 mM), autoxidation occurred at all pH values investigated between 4·0 and 9·0. Over the pH range 5·5 to 9·0, the reaction was extremely rapid, with a half-life of less than 5 s. Thus, when *ferrous* sulphate was added to methyldopa at pH 7·0, a visible spectrum identical to that of the purple *ferric* iron-methyldopa complex was observed within 10 s.

However, at pH 4·0 a much slower and more complicated sequence of events occurred. Slow autoxidation was observed, with the formation of the mono methyldopa-iron complex, which then underwent an internal redox reaction to yield the green semiquinone complex (**4**). The reaction was much slower

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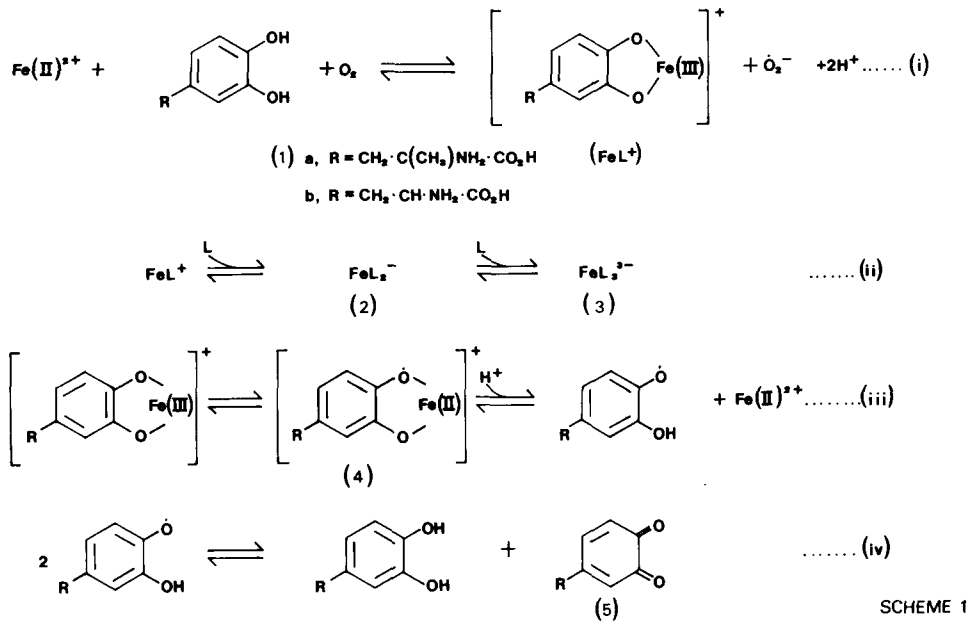


Scheme 1. The reaction of both ferrous and ferric iron with the catechol-containing compounds, methyldopa (**1a**) and levodopa (**1b**).

than that observed at neutral pH values (Fig. 2), and possessed a half-life in excess of 30 min. A similar rate was observed with levodopa (Fig. 2). At pH values in the region of 2·0, there was little autoxidation of ferrous iron, and consequently virtually no interaction with either methyldopa or levodopa.

Discussion

The autoxidation of ferrous iron and the subsequent reduction of ferric iron by both methyldopa and levodopa back to ferrous iron at pH 4·0, indicates that, *in principle*, redox cycling (Scheme 1) can occur in the stomach. Thus, depending on the period of time methyldopa resides in the stomach, a considerable portion is predicted to be converted to the inactive quinone derivative (**5**). Although the reaction is not fast, appreciable redox cycling will occur after a period of 1 h. Methyldopa possesses an extremely high affinity for ferric iron, and therefore the autoxidation process is not inhibited in the presence of ligands likely to be present in the diet, such as phytic acid, phosphate, amino acids and citrate (results not presented). When the ferrous salts and methyldopa leave the stomach, the environment of the duodenum and jejunum (pH $\geq$6·0) is such that within 10 s, all the iron will be oxidised to the ferric state, and will, therefore, bind extremely tightly to two molecules of methyldopa. This highly charged complex (**2**) possesses a molecular weight over 500, and thus, methyldopa bound to ferric iron is predicted to be poorly absorbed from the small intestine (Lieb & Stein 1971). The 3:1 methyldopa-iron complex (**3**) only forms to an appreciable extent at pH values above 8·5 (Fig. 1). In the clinical trials described by Campbell et al (1988), 500 mg of methyldopa (2·37 mmol) was administered with 325 mg of ferrous sulphate (1·16 mmol). As each iron atom will bind two molecules of methyldopa, there is potential for up to 98% of the methyldopa dose becoming bound to iron, and hence rendered unavailable for

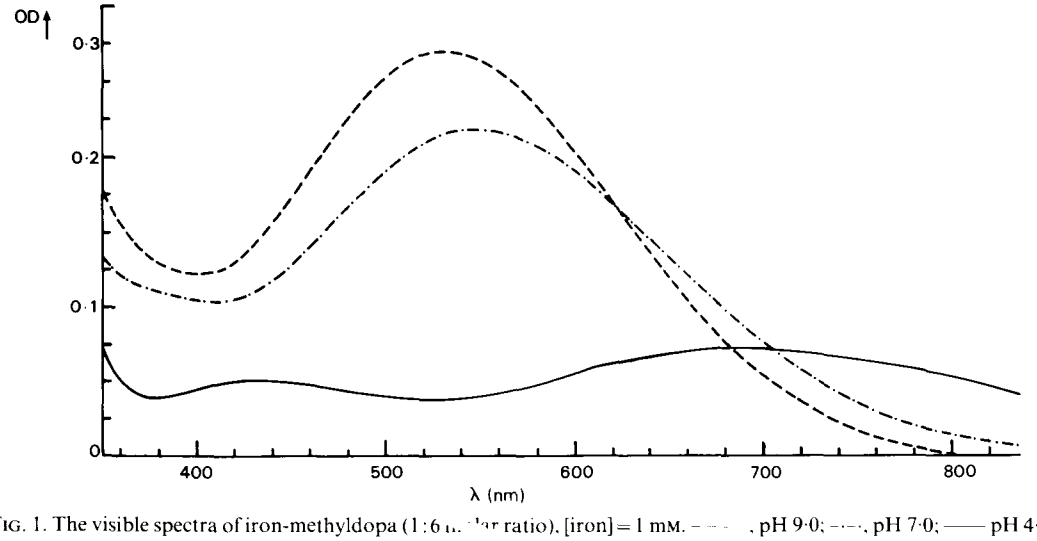


FIG. 1. The visible spectra of iron-methyldopa (1:6 molar ratio), [iron] = 1 mM. - - - , pH 9·0; -·-·, pH 7·0; —— pH 4·0.

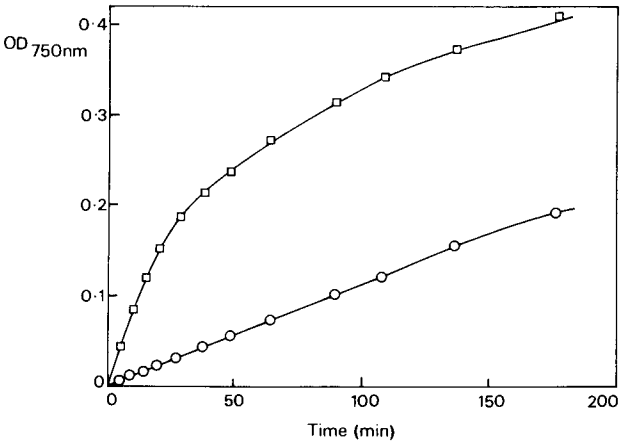
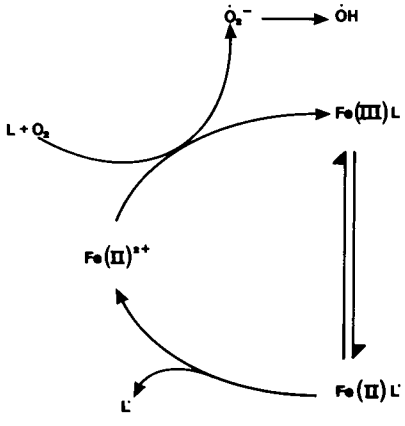


FIG. 2. The time course of the reaction of ferrous iron with, □, methyldopa and ○, levodopa at pH 4·0 (50 mM sodium acetate). [Iron] = 1 mM; [methyldopa] = [levodopa] = 6 mM.

intestinal absorption. The bioavailability of methyldopa will, therefore, be appreciably reduced in the presence of iron (II) *via* two independent mechanisms; redox cycling in the stomach and stable complex formation in the small intestine. Identical arguments hold for levodopa (Mentasti et al 1976).

Of the three dopa metabolites reported by Campbell et al (1988), only α-methyldopamine is capable of triggering iron autoxidation. Significantly, the urine levels of both this metabolite and methyldopa fell to less than 25% of the level detected when methyldopa was administered in the absence of ferrous salts. In contrast, the two metabolites which cannot bind iron (III) with high affinity, methyldopa sulphate and α-methyldopamine sulphate are reduced by a much lesser extent ($\approx 70\%$). This finding is best explained by the chelation of iron not only occurring in the lumen of the gastrointestinal tract, but also in the epithelial cells. It is clear, as previously discussed by Campbell et al (1988), Campbell & Hasinoff (1989) and Stockley (1989), that there are strong interactions between both levodopa and methyldopa and iron.



SCHEME 2

Scheme 2. The redox cycling of iron catechol (FeL) moieties. The net effect is the production of the hydroxyl radical and the disproportionation of the semiquinone (L·) to quinone and the parent catechol.

Iron deficiency anaemia is not a particular problem with Parkinsonian patients, and thus the levodopa/iron interaction described in this paper is unlikely to be encountered frequently. In contrast, the co-prescription of methyldopa and iron is not uncommon. Although methyldopa is no longer generally recommended as first or second line therapy in mild to moderate essential hypertension (Simpson 1987), it is still widely prescribed in general practice in the UK, accounting for about 22% of the 9 million prescriptions written for antihypertensive medication in 1988. Furthermore, it is still regarded as having a useful role in situations where other antihypertensives may be contra-indicated, such as renal impairment and pregnancy, and in the elderly, who tolerate it well. With geriatric patients, methyldopa is likely to be long term therapy, as might the iron in a patient whose diet is thought inadequate. Failure to control blood pressure could precipitate a stroke. Pregnant women routinely take iron supplements, and those requiring antihypertensive medication to prevent pre-eclampsia could develop severe complications.

A satisfactory dosage regime to avoid co-administration would not be easy to devise, because both drugs need to be taken in divided doses. Methyldopa is usually taken 2 or 3 times daily, to maintain smooth hypotensive control, and the required daily dose of iron must be divided if gastric upset is to be avoided (single daily dose delayed release forms would, of course, be prey to the same interactions as multiple dosing). Only in prophylactic therapy with iron, might a single dose of standard preparations such as ferrous sulphate or gluconate be sufficient. Moreover, the development of special formulations which overcome the incompatibility is unlikely to be profitable, since so many alternative antihypertensives are available.

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