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ORIGINAL PAPER

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Intravenous antidepressant treatment: focus on citalopram

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Abstract During the last decade, the number of patients who consult primary care physicians or psychiatrists for symptoms of depression has doubled. The majority of depressed patients are prescribed oral medication; however, in several European countries antidepressant therapy may be initiated with a daily intravenous infusion. The choice of intravenous antidepressants was previously limited to agents such as dibenzepine, doxepin, clomipramine and viloxazine. More recently, the selective serotonin reuptake inhibitor (SSRI) citalopram has been administered as an intravenous infusion to severely depressed patients. The results from both open and double-blind clinical studies with intravenous citalopram suggest that it is an effective and well-tolerated treatment for depression. Moreover, when treatment is initiated by infusion and continued orally, citalopram is at least as effective as clomipramine, doxepin and viloxazine. As with oral treatment, adverse events experienced by patients are mild to moderate in severity with 50 % of patients reporting no adverse events. The high bioavailability of citalopram indicates that the switch from intravenous to oral citalopram would prevent a deterioration of symptoms as plasma drug concentrations would be maintained. Thus citalopram, the only SSRI available as an intravenous formulation, may be a useful addition for the treatment of severely depressed patients who may benefit from more intensive therapy. The aim of this paper is to review available data detailing the clinical outcome of intravenously administered citalopram in depressed patients.

Key words citalopram · infusion · viloxazine · clomipramine · SSRI · antidepressant

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Introduction

Depression is a common, chronic and debilitating illness that is characterised by episodes of relapse and recurrence (Montgomery 1997). The lifetime prevalence of depression has been estimated to be approximately 17 % (Angst 1999). Although depression is among the most prevalent of psychiatric conditions, a significant proportion of patients (43 %) in the community fail to seek medical help (Lépine et al. 1997). Indeed, the DEPRES study revealed that of the 57 % of depressed patients who did seek help, only 25 % were prescribed antidepressants (Lépine et al. 1997). Some patients are hospitalised as a consequence of depression. These patients tend to be either elderly or more severely depressed. Antidepressant treatment for these patients is usually in the form of oral agents; however, intravenous antidepressants are used in several European countries (Laux et al. 1997).

Although intravenous administration of antidepressants such as clomipramine (Faravelli et al. 1983; Pollock et al. 1989; Sallee et al. 1997), dibenzepine (Gastpar et al. 1984), doxepine (Laux et al. 1989; Adler et al. 1997), viloxazine (Bouchard et al. 1997) and citalopram (Charbonnier et al. 1987; Schöny 1992; Svestka et al. 1993a, b; Bouchard et al. 1997; Baumann et al. 1998; Guelfi et al. 2000) has been used mainly in Europe, there are relatively few studies and the additional benefits conferred by parenteral versus oral administration are still debated. The clinical deterioration observed when switching intravenous antidepressant treatment to oral treatment (Brückmann & Blaha 1982; Wolfersdorf et al. 1984) has been postulated to be due to a reduction in the plasma level of active drug, possibly due to poor compliance with oral therapy (Adler et al. 1997).

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Early results from open studies (Kielholz 1982, 1984), later confirmed by controlled studies with maprotiline (Wolfersdorf et al. 1984), doxepin (Laux et al. 1989; Adler et al. 1997) and clomipramine (Faravelli et al. 1983; Pollock et al. 1989; Sallee et al. 1997), indicated a more rapid onset of action with intravenous administration of antidepressant compared with oral administration. Recently, this has also been suggested for mirtazapine in an open trial (Konstantinidis et al. 2002). Parenteral administration avoids first-pass metabolism and lower doses of antidepressants are needed to achieve the same plasma levels compared with oral administration. In addition, the presence of active metabolites may also influence sustained clinical improvement of depressed patients following oral medication. For example, the metabolite of maprotiline is inactive and this may account for the clinical deterioration observed following a switch from infusion to oral treatment, since active drug concentration in plasma would be reduced (Wolfersdorf et al. 1984) unless the dose is appropriately adjusted. In contrast, the metabolite of clomipramine is active (with a different pharmacodynamic profile) and may account for the continued, although less rapid, clinical improvement observed with oral medication (Wolfersdorf et al. 1984). Furthermore, compliance with parenteral antidepressant treatment is not an issue. Also, the contribution of the psychological component of treatment should not be underestimated. The increased monitoring and the intense care provided by the healthcare team is thought to play a significant role in supporting therapeutic efficacy (Bouchard et al. 1997).

Older studies with parenteral antidepressants have largely been conducted using tri- or tetracyclic antidepressants which themselves, although effective treatments, have specific side-effect disadvantages. Intravenous infusion of clomipramine and doxepin have been found to be efficacious in the treatment of depressed patients. In a double-blind, randomised study in which patients received intravenous or oral clomipramine, there was no difference in the response rate; for both routes of administration, 7/11 patients showed a ≥ 50 % reduction in the Hamilton Depression Rating Scale (HAM-D) total score (Hamilton 1960) at the end of the study period (Pollock et al. 1989). Clomipramine was also reported to reduce HAM-D scores by ≥ 50 % in 44 % of therapy-resistant adolescent depressed patients (Sallee et al. 1997). One double-blind, randomised study evaluated the efficacy of doxepin administered by intravenous infusion alone (27 patients) with intravenous infusion followed by oral therapy (27 patients) (Adler et al. 1997). The response rate (i. e. improvement in Clinical Global Improvement (CGI) scale (Guy 1976) score as 'very good' or 'good') was similar in both treatment groups: 75 % for the intravenous group and 77 % for the intravenous-oral group (Adler et al. 1997).

The advent of the SSRIs, which offered similar efficacy with a reduced side-effect profile, expanded the choice of antidepressants for a wide range of depressed patients. Citalopram is the most selective SSRI (Hyttel et al. 1995; Stahl 1998) and has been shown to be an effective and well-tolerated antidepressant (Noble and Benfield 1997). It is also the only SSRI that is available as an intravenous formulation, thus providing another treatment option for depressed patients in need of more intensive care.

The aim of this paper is to review available data detailing the clinical outcome of intravenously administered citalopram in depressed patients.

Clinical studies with citalopram

A literature search identified seven citalopram studies (four open, three double-blind) which assessed a total of 1357 hospitalised patients with a diagnosis of major depressive disorder (DSM-III-R; American Psychiatric Association 1987). Of the total number of patients, 617 patients were treated with intravenous citalopram. The studies compared the efficacy and tolerability of citalopram (normally 40 mg, range 10–80 mg) with placebo, oral citalopram (20–60 mg), or viloxazine (300–600 mg).

A total of 422 hospitalised patients were treated with citalopram infusions in open studies which lasted up to three weeks (Charbonnier et al. 1987, Schöny 1992, Svestka et al. 1993a, b), while 195 patients entered double-blind, randomised controlled studies (2 placebo-controlled: Baumann et al. 1998; Guelfi et al. 2000; and one comparator-controlled: Bouchard et al. 1997) lasting up to two weeks. Both adult and elderly patients were included in the studies.

Measures of treatment efficacy in these studies included the HAM-D scale (17 or 21 items), the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg 1979) and the CGI scale. In most cases, patients were diagnosed as suffering from severe depression with baseline HAM-D total scores ≥ 22 (Pollock et al. 1989) or baseline MADRS total scores of ≥ 30 (Schöny 1992; Bouchard et al. 1997; Guelfi et al. 2000). Response to treatment in these studies was defined as a ≥ 50 % reduction in HAM-D or MADRS scores.

Efficacy

Early open studies with intravenous citalopram demonstrated treatment efficacy (Table 1). The first published study showed that following three weeks of treatment with citalopram by infusion alone, 41 % of patients were in complete remission as assessed by a MADRS total score of ≤ 5, whilst 24 % of patients exhibited a partial response (MADRS total score 6–15) (Charbonnier et al. 1987). However, in another open study, the proportion of patients who were reported to have fully remitted following intravenous citalopram followed by oral citalopram was 69 % (Svestka et al. 1993a). Of those patients who received citalopram orally, 62 % were reported to be fully remitted (Svestka et al. 1993a). Similar remission

Table 1 Open studies: response rates for patients receiving intravenous, followed by oral, citalopram

Study design	Study duration (weeks)	No. of patients in IV-oral group	Responders[f] (%) after 10–14 days' IV treatment	Responders[f] (%) after IV and oral treatment	Remission (%)
Citalopram (20–60 mg by iv infusion), hospitalised patients aged 19–70 years[a]	3	49	41[d]	NA	–
Citalopram (iv 14 days + oral 14 days; mean maximum dose 50 mg/day), hospitalised patients, mean age 54 years[b]	4	32	47	–	69[e]
Citalopram (iv 14 days + oral 14 days; mean maximum dose 53 ± 25 mg/day); hospitalised patients, mean age 50 years[c]	4	57	47*	–	60[e]
Citalopram (iv 10–14 days + oral 4 weeks; average dose 40 mg/day), hospitalised and primary care patients aged 17–92 years[d]	4–6	284	–	68	–

[a] Charbonnier et al. (1987); [b] Svestka et al. (1993a); [c] Svestka et al. (1993b); [d] Schöny (1992); [d] MADRS ≤ 5 defined as a complete response; [e] no criteria given for remission. *IV* intravenous infusion; *NA* not applicable; [f] Response is defined as a ≥ 50 % reduction in MADRS or HAM-D total score. * significantly improved ($p < 0.02$) after 1 week

rates (60 % and 59 %) were observed in an earlier smaller study (Svestka et al. 1993b). A significant reduction in HAM-D–21 score was observed after 7 days infusion treatment period ($p \leq 0.05$) (Svestka et al. 1993a). Of the 765 patients who entered a large, open, post-marketing study, 284 patients received intravenous citalopram for the first 10–14 days, with a response rate of 68 % after 4–6 weeks (Schöny 1992).

Double-blind, randomised controlled studies in 376 patients (195 on infusion) confirm the findings of the open studies (Bouchard et al. 1997; Baumann et al. 1998; Guelfi et al. 2000) (Table 2). In the study of Baumann et al. (1998), the proportion of responders (defined as having a reduction in HAM-D–17 total score of ≥ 50 %) was similar (not significantly different) between treatment groups (67 % in the infusion group and 63 % in the oral group). However, a significant difference was observed in the results of the double-blind, randomised controlled study of Guelfi et al. (2000): at study end, 77 % of patients in the infusion group had ≥ 50 % reduction in MADRS total score compared with only 65 % of patients in the oral group ($p < 0.05$). In a further study, citalopram infusion followed by oral citalopram was shown to be significantly better than intravenous and oral viloxazine, with response rates of 80 % and 69 %, respectively (Bouchard et al. 1997).

Onset of effect

Open studies have consistently indicated that citalopram infusion may offer a more rapid onset of efficacy. A significant reduction of MADRS total score was, in fact, observed after one week of treatment in the Charbonnier et al. (1987) study. Svestka et al. (1993a) also reported significantly more infusion-treated patients (47 %) having improved fully or partially after one week compared with patients given tablets (24 %, $p < 0.05$). Similar results were obtained in a second study by this group (Svestka et al. 1993b), where 27 patients in the infusion group compared with 12 patients in the tablet group were significantly improved after one week ($p < 0.02$). Furthermore, the onset of action in this study was reported to be significantly faster in the infusion

Table 2 Placebo-controlled studies: comparison of response rates for patients receiving intravenous, followed by oral antidepressants or oral followed by oral antidepressants

Study design	Study duration (weeks)	No. of patients per group	Reduction in depression rating scale[d] score after first treatment phase		Responders[e] (%) at treatment end	
			IV-oral	Oral-oral	IV-oral	Oral-oral
Citalopram (40 mg iv 10 days + oral up to 42 days) in hospitalised patients (mean age 40 years)[a]	6	30+30	8.3	6.7	67	63
Citalopram (40 mg iv 8 days + oral 34 days) in hospitalised patients (mean age 43 years)[b]	6	135+119	19.4	18.8	77	65
Citalopram (40 mg iv 14 days + oral 28 days vs viloxazine300 mg iv 14 days + 600 mg oral 28 days) in hospitalised patients aged 18–70 years[c]	6	30+32	Citalopram 21.7 Viloxazine 17.1	NA NA	80% 69%	NA NA

[a] Baumann et al. 1998; [b] Guelfi et al. 2000; [c] Bouchard et al. 1997; [d] MADRS for Guelfi et al. and Bouchard et al., HAM-D for Baumann et al.; [e] Response is defined as a ≥ 50 % reduction in MADRS or HAM-D total score. *IV* intravenous infusion; *NA* not applicable

group (9.9 days) than in the tablet group (12.7 days, $p < 0.05$). In the Schöny study (1992), an average reduction in total MADRS score of 34 % was reported following the infusion period compared with 27 % following administration of tablets.

These data have been confirmed in double-blind studies using double-dummy techniques to control for psychological factors. In the Baumann et al. study (1998), the percentage of patients with a rating of 'much' or 'very much' improved was higher for the group receiving active citalopram infusion (50 %) than for the group receiving active tablets (36.7 %), which suggested, according to the authors, a "tendency toward a quicker onset of action". Likewise, more treatment responders (defined as ≥ 50 % reduction of the HAM-D total score) were observed following infusion for 11 days than after treatment with tablets (33.3 % vs 17.9 %, respectively, and not reaching statistical significance). The recent Guelfi et al. study (2000) confirmed these strong trends: improvements in CGI scale scores were reported for significantly more patients in the active infusion group than in the tablet group after one week ($p = 0.017$). There were no apparent differences between the group in MADRS score at day 8, but following that assessment the slope of reduction in MADRS total score was significantly greater in the infusion group (a –2.8 point difference, $p = 0.015$).

Tolerability

There were no differences in the incidence and severity of adverse events reported by patients in the infusion or the oral groups during the studies (Charbonnier et al. 1987; Schöny 1992; Svestka et al. 1993a; Adler et al. 1997; Bouchard et al. 1997; Baumann et al. 1998; Guelfi et al. 2000). Indeed, in three of the four open citalopram studies, ≥ 50 % patients reported no adverse events during therapy with citalopram (Svestka et al. 1993a, b; Schöny 1992). Of the patients who did experience side effects, tremor, somnolence and dizziness were reported by ≥ 10 % (Charbonnier et al. 1987). The most common adverse events associated with citalopram treatment in the double-blind, randomised studies were nausea, headache, tremor, and somnolence (Bouchard et al. 1997; Baumann et al. 1998; Guelfi et al. 2000). The observed side effects were typically class effects and were not related to the route of administration.

Standard laboratory investigations and electrocardiogram (ECG) analyses (Kovács et al. 2000) indicated no clinical abnormalities associated with citalopram infusion.

Conclusions

To date, citalopram is the only selective serotonin reuptake inhibitor which is available both as an intravenous and oral formulation. Open and double-blind, randomised, controlled clinical studies have shown that citalopram infusion followed by citalopram oral medication is an effective and well-tolerated treatment for severely depressed patients (Charbonnier et al. 1987; Schöny 1992; Svestka et al. 1993a, b; Bouchard et al. 1997; Baumann et al. 1998; Guelfi et al. 2000). Indeed, similar response rates were observed for citalopram as for clomipramine (Pollock et al. 1989; Sallee et al. 1997), doxepin (Adler et al. 1997) and viloxazine (Bouchard et al. 1997). The controlled citalopram studies indicate that initial infusion therapy may lead to faster onset of antidepressant action or possibly better treatment outcome, particularly for the severely depressed (Guelfi et al. 2000). The improved tolerability profile of the SSRIs also suggests that citalopram would be a good alternative to tricyclic antidepressants. In addition, the pharmacokinetic profile of citalopram shows a high oral bioavailability (Baumann and Larsen 1995) which suggests that plasma levels of citalopram are maintained (without dose adjustment) following the switch from infusion to oral therapy, thus reducing the possibility that clinical deterioration would occur once oral therapy commenced, as has been reported for other antidepressants (Brückmann & Blaha 1982; Wolfersdorf et al. 1984).

In conclusion, patients in need of more intensive care and treatment may benefit from initial slow-drop infusion of citalopram and continued oral treatment, an issue which has to be studied further in randomised controlled trials.

References

1. Adler L, Hajak G, Lehmann K, Kunert HJ, Hoffmann G, Issinger J, Boke J, Huether G, Ruether E (1997) On the problems of switching from intravenous to oral administration in drug treatment of endogenous depression. Pharmacopsychiatry 30:62–69
2. American Psychiatric Association (APA) (1987) Diagnostic and statistical manual for mental disorders, 3rd edition (revised). Washington DC: American Psychiatric Association
3. Angst J (1999) Major depression in 1998: are we providing optimal therapy? J Clin Psychiatry 60 (Suppl. 6):5–9
4. Baumann P, Larsen F (1995) The pharmacokinetics of citalopram. Rev Contemp Pharmacother 6:287–295
5. Baumann P, Nil R, Bertschy G (1998) A double-blind, double-dummy study of citalopram comparing infusion versus oral administration. J Affect Disord 49:203–210
6. Bouchard JM, Strub N, Nil R (1997) Citalopram and viloxazine in the treatment of depression by means of slow drop infusion. A double-blind comparative trial. J Affect Disord 46:51–58
7. Brückmann JU, Blaha L (1982) Katamnestische Beurteilungen des Therapieerfolges antidepressiver Infusionsbehandlung. In: Kielholz P, Adams C (eds) Antidepressive Infusionstherapie. Stuttgart, New York: Georg Thieme, pp 26–35
8. Charbonnier JF, Reboul P, Rougier M, Aubin B, Chassaing JL, Philippe P, Planche R, Hoepfner Petersen HE (1987) Citalopram: an open trial of a highly selective 5-HT uptake inhibitor, administered intravenously to depressed patients. L'Encephale XIII:249–254
9. Faravelli C, Broadhurst AD, Ambonetti A, Ballerini A, De Biase L, La Malfa G, Das M (1983) Double-blind trial with oral versus intravenous clomipramine in primary depression. Biol Psychiatry 18:695–706

10. Gastpar M, Cornu F, Faessler J, Haefliger A, Keller H, von Lerber W, Pagan J, Rem J (1984) Efficacy and tolerability of dibenzepine administered by intravenous drip infusion to severely depressed patients. Neuropsychobiology 11:44–48
11. Guelfi JD, Strub N, Loft H (2000) Efficacy of intravenous citalopram compared with oral citalopram for severe depression: safety and efficacy data from a double-blind, double-dummy trial. J Affect Disord 58:201–209
12. Guy A (1976) ECDEU Assessment Manual for Psychopharmacology. Rockville, Maryland: US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration
13. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
14. Hyttel J, Arnt J, Sanchez C (1995) The pharmacology of citalopram. Rev Contemp Pharmacother 6:271–285
15. Kielholz P (1982) Eine kombinierte antidepressive Infusionstherapie. In: Kielholz P, Adams C (eds) Antidepressive Infusionstherapie. Stuttgart, New York: Georg Thieme, pp 1–5
16. Kielholz P (1984) Zum Thema. In: Kielholz P, Adams C (eds) Tropfinfusionen in der Depressionsbehandlung. Stuttgart, New York: Georg Thieme, pp 1–7
17. Konstantinidis A, Stastny J, Ptak-Butta J, Hilger E, Winkler D, Barnas C, Neumeister A, Kasper S (2002) Intravenous mirtazapine in the treatment of depressed inpatients. Eur Neuropsychopharmacol 12:57–60
18. Kovács G, Kelemen É, Király L (2000) Cardiologic relations of citalopram drop infusion therapy. Eur Neuropsychopharmacology 10 (Suppl 3):S255 (P.1.091)
19. Laux G, König W, Baumann P (1997) Infusionstherapie bei Depressionen: Ein Leitfaden fur Klinik und Praxis. 4. Aufl: Hippokrates
20. Laux G, König W, Lesch KP, Stein A (1989) Intravenous versus oral treatment of endogenously depressed patients with doxepin. A double-blind study with plasma level determination. Wien Med Wochenschr 139:525–529
21. Lépine JP, Gastpar M, Mendlewicz J, Tylee A, on behalf of the DEPRES Steering Committee (1997) Depression in the community: the first Pan-European study in DEPRES (Depression Research in European Society). Int Clin Psychopharmacol 12:19–29
22. Montgomery SA (1997) Reboxetine: additional benefits to the depressed patient. J Psychopharmacology 11:S9–S15
23. Montgomery SA, Åsberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389
24. Noble S, Benfield P (1997) Citalopram: a review of its pharmacology, clinical efficacy and tolerability in the treatment of depression. CNS Drugs 8:410–432
25. Pollock BG, Perel JM, Nathan RS, Kupfer DJ (1989) Acute antidepressant effect following pulse loading with intravenous and oral clomipramine. Arch Gen Psychiatry 46:29–35
26. Sallee FR, Vrindavanam NS, Deas-Nesmith D, Carson SW, Sethuraman G (1997) Pulse intravenous clomipramine for depressed adolescents: double-blind, controlled trial. Am J Psychiatry 154:668–673
27. Schöny W (1992) Efficacy and tolerability of citalopram in comparison of parenteral and oral application. Neuropsychiatrie 6:65–71
28. Stahl SM (1998) Using secondary binding properties to select a not so selective serotonin reuptake inhibitor. J Clin Psychiatry 59:642–643
29. Svestka J, Cesková E, Kamenicka V, et al. (1993a) Comparison of intravenous and peroral administration of citalopram in the treatment of major depression. Homeostasis 34:204–205
30. Svestka J, Cesková E, Kamenicka V, Buresova A, Obrovska V, Synek O (1993b) Citalopram (Seropram) in tablet and infusion forms in the treatment of major depression. Cesk Psychiatr 89:331–339
31. Wolfersdorf M, Wendt G, Binz U, Metzger BR, Hole G (1984) Zum Problem der Umstellung von antidepressiver Infusionstherapie auf perorale Medikation. In: Kielholz P, Adams C (eds) Tropfinfusionen in der Depressionsbehandlung. Stuttgart, New York: Georg Thieme, pp 105–115