

Control of severe pain with sustained-release morphine tablets v. oral morphine solution

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Recently a sustained-release morphine sulfate tablet (MS Contin [MSC]) was introduced in Canada. In a randomized double-blind crossover trial we compared MSC given every 12 hours with a morphine sulfate solution (MSS) given every 4 hours to 17 patients suffering from chronic severe pain. After titration of the morphine dosage to optimize the analgesic effect, each patient received 10 days of therapy with either MSC or MSS, then 10 days of therapy with an equal daily dose of the other formulation. Both preparations provided effective pain control, with minimal side effects. There was no significant difference between MSC and MSS in pain scores on a visual analogue scale (VAS), severity scores for tiredness and nausea, amount of supplemental morphine needed for breakthrough pain or patient preference. The plasma morphine concentrations tended to be greater during treatment with MSC. The study had an 89% probability of detecting a clinically significant difference in VAS pain scores. We conclude that an individualized, twice-daily regimen of MSC is as effective as MSS given every 4 hours for control of severe pain. The twice-daily regimen has several advantages: it provides for an uninterrupted night's sleep, it is substantially more convenient than the six doses per day required with MSS, and it should help reduce both medication errors and noncompliance.

Le MS Contin (MSC), comprimé de sulfate de morphine à libération graduelle, est depuis peu

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disponible au Canada. Dans un essai croisé à double insu sur des sujets désignés au hasard, on compare l'effet du MSC aux 12 heures à celui de la solution de sulfate de morphine (SSM) aux 4 heures chez 17 malades souffrant de douleur chronique grave. Après titrage posologique à la recherche de l'effet analgésique optimum, on administre à chaque malade, consécutivement, l'une et l'autre de ces formules, à doses quotidiennes égales, pendant 10 jours chacune. On réalise une analgésie efficace dans ces deux modalités, avec très peu d'effets secondaires. Elles ne diffèrent significativement ni quant à un indice analogique visuel de la douleur dit VAS, ni quant à l'indice de gravité de la fatigue ou de la nausée, ni quant au besoin éventuel d'un supplément de morphine pour douleur survenant entre les doses prévues, ni quant à la préférence des malades. Le MSC tend à donner de plus fortes morphinémies. La probabilité de déceler ici une différence cliniquement significative dans l'indice VAS était de 89%. On conclut qu'un régime individualisé à base de MSC deux fois par jour est aussi efficace, pour juguler la douleur grave, que la SSM aux 4 heures. Il a l'avantage de ne pas interrompre le sommeil de nuit et d'être plus simple à mettre en oeuvre. On peut croire qu'il en résultera une diminution des erreurs médicamenteuses et de l'indocilité des malades.

The treatment of chronic severe pain is frequently inadequate.¹⁻⁴ Inadequate pain control can lead to unnecessary suffering and impairment of psychologic support and may prevent meaningful communication between dying patients, their families and the health care team at the very time when communication is most needed. Although the incidence of inadequate pain management in Canada has not been directly studied, the Department of National Health and

Welfare's Expert Advisory Committee reported that up to 25% of patients with cancer die without adequate pain relief.^{5,6} Causes of suboptimal pain control may be related to lack of appropriate services, belief that cancer is inevitably accompanied by pain, failure to recognize the existence of pain or to adequately assess its components, and, too frequently, inadequate or inappropriate use of analgesics.

Orally given nonopioid, opioid and adjuvant analgesics are the principal therapies for cancer pain.^{2,4,6} A common approach has been to use a "three-step analgesic ladder" in which nonopioids, weak opioids and strong opioids are progressively used in response to increasing severity of pain. In a retrospective study of 1229 patients with cancer pain Ventafridda and colleagues⁷ found that 70.9% were treated successfully with this approach. The remaining patients required neurolytic procedures in addition to the oral analgesics.

Orally administered morphine is the most commonly used strong opioid and when used in regularly scheduled individualized dosages has been shown to provide effective pain relief in 75% to 90% of patients with chronic severe pain.⁸⁻¹⁰ The common aqueous morphine solutions can be difficult to use since they must be given on a fixed schedule, every 4 hours, for optimal efficacy.¹¹ Sustained-release morphine sulfate tablets (MS Contin [MSC], Purdue Frederick Inc., Toronto), in which morphine is incorporated into a wax-cellulose matrix delivery system, were developed to provide a controlled rate of release of morphine, so that the tablets could be given every 12 hours. Sustained-release formulations of other drugs are well established and have been shown to improve efficacy, compliance, convenience and patient acceptability.^{12,13}

We performed a randomized double-blind crossover trial to compare the efficacy of MSC and orally given morphine sulfate solution (MSS) in patients with chronic severe pain.

Methods

We reviewed our hospital's pharmacy records to identify patients from the acute care medical and surgical wards or the community care nursing service who were receiving analgesic regimens equal to or greater than 60 mg/d of orally given morphine. Patients over 19 years of age with a diagnosis consistent with chronic severe pain were considered eligible. Patients were excluded if they were unsuitable for therapy with orally given morphine, had a history of widely fluctuating pain severity necessitating parenteral administration of opiates or were scheduled to receive chemotherapy or radiation therapy within 1 month. The study was approved by the Pharmacy and Therapeutics Committee of Kelowna General Hospital, Kelowna, BC, and the Bureau of Human Prescription Drugs, Department of National Health and Welfare. All

patients gave written informed consent, and agreement to their participation was received from their family physician.

The test medications were 30-mg, 60-mg and 100-mg tablets of MSC and 5 mg/mL of MSS, prepared by the hospital pharmacy. MSC was administered every 12 hours (at 7 am and 7 pm); MSS was administered every 4 hours (starting at 7 am). Matching placebos were used to maintain blindness. Each patient was given a separate supply of active MSS for use as necessary to control episodes of breakthrough pain.

No analgesics other than the test medications and the MSS for breakthrough pain were allowed during the study. Treatment with nonanalgesic medications that had been part of the patient's regular therapy was continued at stable dosages throughout the trial. A bowel routine with a stimulant and stool softener was prescribed for all the patients.

All the patients first entered a morphine dosage titration period. Titration was performed under double-blind conditions with either MSC or MSS, as determined by means of random allocation. We calculated each patient's initial total daily morphine dose from the prestudy analgesic regimen using an analgesic equivalency chart.⁶ The daily morphine dose was then adjusted, as necessary, for optimal pain control with minimal or no sedation. Increases in morphine doses were separated by 48 hours, the time required to re-establish "steady-state" conditions with the sustained-release tablets. Throughout the titration period the patients were allowed to use extra MSS for management of breakthrough pain. The titration period was considered complete when the patient's pain was well controlled, no dosage adjustment had been needed for 3 days and the average daily intake of extra MSS for breakthrough pain did not exceed 50% of the daily dose provided by the test formulations.

The patients then entered a two-phase crossover period in which they completed two successive 10-day treatment phases starting with either MSC or MSS, as determined by means of random allocation. Further dosage adjustment was not allowed; however, the patients were encouraged to use their extra MSS for any breakthrough pain. Thus, with the exception of the extra morphine, each patient's daily morphine dose was the same during the MSC and MSS treatment phases.

We recorded pain intensity at 7 and 11 am and at 3, 7 and 11 pm each day using a visual analogue scale (VAS) and the present pain intensity (PPI) index of the McGill-Melzack Pain Questionnaire.⁸ The VAS consisted of a 10-cm-long horizontal line with the words "no pain" and "excruciating pain" at either end. The patients placed a mark on the line that corresponded with the severity of their pain, and the distance in centimetres from the mark to the "no pain" end of the line was their score. The PPI rating consists of six adjectives: no pain (0), mild (1), discomforting (2), distressing (3),

horrible (4) and excruciating (5). We recorded the side effects of nausea, vomiting, dizziness, tiredness, confusion and dry mouth daily at 7 pm using a verbal scale from 0 (none) to 6 (intolerable).¹⁴ The time and amount of each dose of extra MSS needed for breakthrough pain was recorded, as were all changes to the patients' treatment with nonanalgesic medications. On the last day of the study, while still blinded to medication, the patients were asked to express an overall preference for phase 1 or phase 2.

Blood samples for morphine analysis were obtained at 7 am and 12 noon on the last 3 days of both treatment phases. The sample obtained at 7 am was taken immediately before dosing to measure the minimum plasma morphine concentration. Noon was considered an appropriate time to measure the maximum plasma concentration for both formulations (1 hour after dosing for MSS and 5 hours after dosing for MSC). Plasma morphine analyses were performed in the Faculty of Pharmacy, University of Montreal, with a high-performance liquid chromatography technique.¹⁵

Analysis of variance (ANOVA) for repeated measures was used to test the significance of overall differences between the test medications, times of day and days of treatment for pain scores and for use of extra morphine. This analysis also included tests for interaction between each pair of factors (i.e., test medication and day of treatment). When indicated, multiple comparisons of means

were done with the *t*-test, standard errors being computed from the ANOVA.

ANOVA was used to test for any effects of test medication or day of treatment on the severity of side effects. Patients were also classified as either having or not having side effects. We tested the resulting frequencies for a difference between the preparations using McNemar's chi-squared test.

Overall preference for phase 1 or phase 2 was evaluated by use of Fisher's exact test. We computed the power of the trial to detect differences between the overall mean pain scores, amounts of extra morphine used and severity of side effects using estimates of within-patient variance derived from ANOVA in formulas for the comparison of independent samples.

Results

Of the 29 patients enrolled in the study 11 dropped out, 10 during the titration period and 1 during the crossover period, the reasons being progression of underlying disease (in 4 patients), side effects (in 3), failure to comply with the protocol (in 3) and inability to meet the titration criteria (in 1). The data for one patient who completed the study were excluded from analysis because he received a course of radiation therapy during the study, which markedly affected his pain intensity.

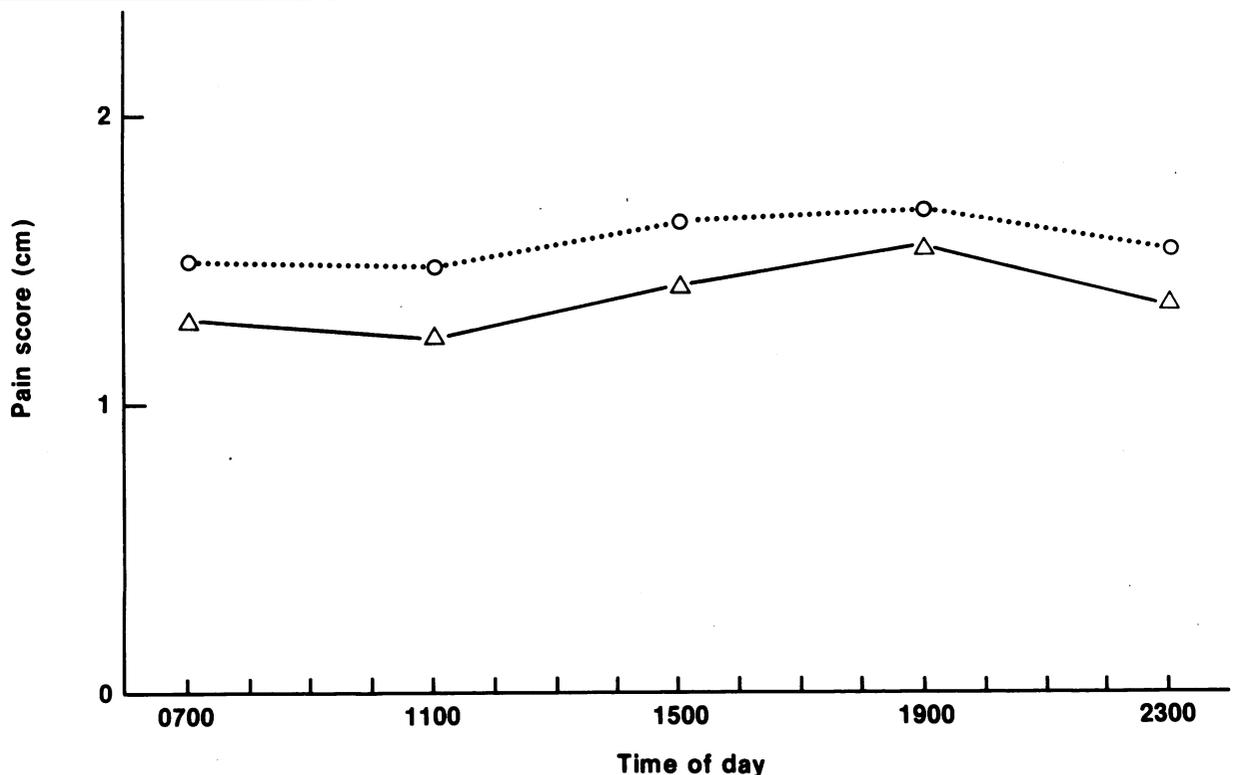


Fig. 1 — Mean pain severity scores, determined on a visual analogue scale (VAS), by time of day, in 17 patients with chronic severe pain during therapy with either MS Contin given every 12 hours (triangles) or morphine sulfate solution given every 4 hours (circles).

The 12 men and 5 women who completed the study had a mean age of 63.0 years and a mean weight of 61.1 kg. Their diagnoses were bowel cancer (in four), lung cancer (in four), stomach cancer (in three), prostate cancer (in two) and, in one patient each, astrocytoma, chronic severe back pain, multiple sclerosis and postherpetic neuralgia. There were no significant differences in demographic features between the patients who received MSC first and those who received MSS first or between the patients who completed the study and those who did not.

During the titration period there was no significant difference in the number of days to titration, the number of dosage adjustments required, the number of episodes of breakthrough pain or the final daily morphine dose between the patients who received MSC and those who received MSS. The daily morphine dose at the end of the titration period was 220.0 (standard deviation [SD] 177.0) mg (extremes 60 and 800 mg).

The overall mean VAS pain scores during treatment with MSC and MSS were 1.36 (SD 1.68) cm and 1.57 (SD 1.82) cm respectively; the difference was not significant. The overall mean PPI scores were 1.05 (SD 0.90) and 1.12 (SD 0.98), the difference also not being significant. There was very close correlation between the VAS and PPI scores, which showed the same trends and conclusions. Therefore, only the VAS scores are reported in more detail.

During both treatment phases the mean VAS pain score was significantly higher ($p < 0.05$) at 7

pm than at 7 or 11 am (Fig. 1). There were no significant trends in the scores over the 10 days of treatment, and none of the differences between the two formulations reached statistical significance (Fig. 2).

During treatment with MSC 84 supplemental doses of morphine were taken, for a total of 2330 mg of morphine. During treatment with MSS 72 supplemental doses were taken, for a total of 2320 mg of morphine. The difference was not statistically significant. Overall, the amount of morphine taken for breakthrough pain represented 6% of the total quantity of morphine taken throughout the study. There was, however, great interpatient variability in the use of supplemental morphine: eight patients received fewer than 3 supplemental doses, whereas four patients required more than 20. The four patients took a total of 110 supplemental doses of morphine, or approximately 70% of the total number of supplemental doses taken by all 17 patients.

To determine whether MSC provided effective pain control for the full 12-hour dosage interval, we analysed the time that supplemental morphine was taken in relation to the 12-hour interval. A total of 34% of the supplemental doses were taken within 4 hours after dosing, 35% were taken 4 to 8 hours after dosing, and 31% were taken 8 to 12 hours after dosing.

We used data for only 11 patients in the analysis of plasma morphine concentrations: the data for 4 patients were excluded because supplemental morphine had been used within 6 hours

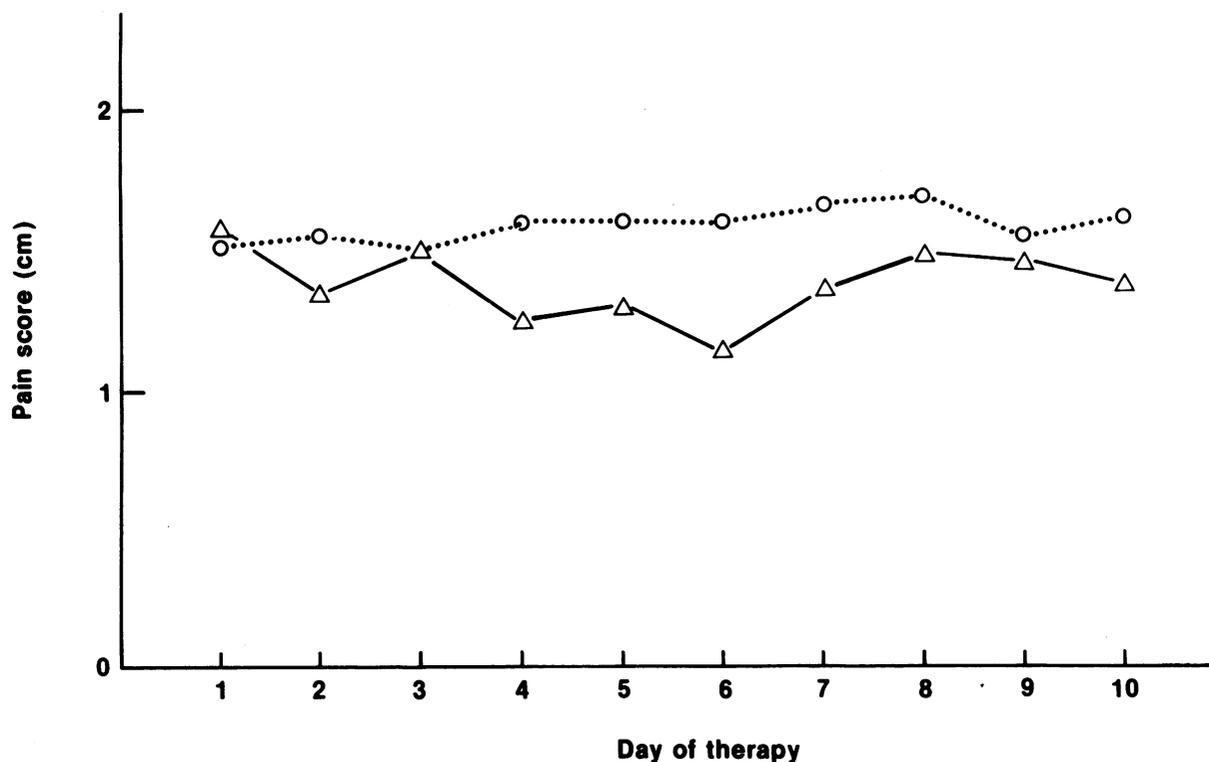


Fig. 2 — Mean VAS pain severity scores, by day of therapy, in the same group of patients. Symbols as in Fig. 1.

before blood sampling, and samples from 2 patients were lost in transit. The mean daily morphine dose for the 11 patients was 174.5 (SD 73.3) mg. The mean maximum plasma morphine concentrations during treatment with MSC and MSS were 47.4 (SD 26.4) and 39.1 (SD 25.7) ng/ml respectively. The mean minimum concentrations were 31.8 (SD 22.6) and 25.7 (SD 22.4) ng/ml respectively. In both cases the level with MSC was significantly greater ($p < 0.05$).

Both MSC and MSS were well tolerated throughout the trial, and the only side effects severe enough to warrant statistical analysis were tiredness and nausea. The mean severity score for tiredness was 0.58 (SD 1.21) during treatment with MSC and 0.64 (SD 1.30) during treatment with MSS. The scores for nausea were 0.44 (SD 1.23) and 0.58 (SD 1.32) respectively. Neither difference was statistically significant. There was no significant difference in the number of patients who experienced side effects during either regimen.

Eight patients preferred the phase of treatment with MSC, six preferred the phase with MSS, and three reported no preference.

Discussion

Our results confirm that regularly scheduled, individualized doses of morphine can provide effective analgesia for patients with chronic severe pain.²⁻⁷ Of the 29 patients who entered our study only the 3 who dropped out because of side effects could be considered to have had a treatment failure. However, two of the three were ultimately able to tolerate orally given morphine when careful titration of the dosage was done outside the constraints of the study. Thus, in clinical practice it appears that the proportion of patients who will not be able to tolerate morphine because of side effects should be small.

Our results also show that chronic severe pain can be as well controlled with twice-daily sustained-release morphine tablets as with morphine solution given six times daily. If we assume that a difference in VAS scores of 0.5 cm would be clinically meaningful, a power calculation reveals that the study had an 89% probability of detecting a difference of that magnitude (at the $p < 0.05$ level of significance) between the two formulations. If a difference of 1.0 cm is considered necessary for clinical significance, the study had a probability of over 99% of detecting a significant difference between the two preparations. The actual difference in mean VAS scores between MSC and MSS was 0.2 cm, which we consider not to be clinically noticeable. This conclusion is supported by the patients' preferences, which were not significantly in favour of either medication. Excellent analgesic efficacy equivalent to that of morphine solution has been reported with MSC given every 12 hours in previous, less controlled studies.¹⁶⁻²³

We emphasize that even though both mor-

phine formulations provided good pain control, it was essential to provide additional morphine for episodes of breakthrough pain. We chose morphine solution for three reasons: first, solution formulations are rapidly absorbed and provide fast pain relief. Second, if episodes of breakthrough pain become frequent enough to warrant an increase in the regularly scheduled dose, the quantity of supplemental morphine used serves as a useful guide in determining the new dose. For example, in a patient receiving 120 mg of MSC per day who regularly requires 60 mg/d of supplemental morphine, an increase in the fixed regimen to 180 mg/d would be appropriate. Third, as a patient's daily morphine requirements are increased, so too must be the dosage for treatment of breakthrough pain. With morphine solution, adjusting the dosage requires only instructing the patient to increase the volume of solution taken.

We chose a dosage of morphine for breakthrough pain equal to the regular dose of morphine received orally every 4 hours, reasoning that a regular dose given every 4 hours was clearly sufficient to be effective and noting published reports that doubling a regular dose (for example, at bedtime) does not result in unacceptable side effects.^{6,18,19} The only patients in whom we did not follow this procedure were those who needed more than 400 mg of morphine per day, for whom we used doses for breakthrough pain equal to 50% of the regular dose given every 4 hours.

The patients did not express a significant preference for either phase of the study. Their preference was indicated while they were still blinded and therefore was limited to their recollection of analgesic efficacy and side effects. This lack of preference further supports our conclusion that MSC given every 12 hours and MSS given every 4 hours provide equivalent analgesia. Both patients and nursing staff expressed a strong preference for the sustained-release tablets for routine clinical use because of the freedom allowed by the twice-daily regimen and the convenience of the tablet formulation. Further, prescribing MSC twice daily reduces both nursing time and costs of drug administration, provides the patient with an uninterrupted night's sleep and allows dosing schedules that are practical for home care and have significantly greater patient acceptance (B.R.G. and W.W.A.: unpublished observations).

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Adult

The recommended dosages of CIPRO® are:

Location of Infection	Type/Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Mild/Moderate	250 mg	q 12h	500 mg
	Severe/Complicated	500 mg	q 12h	1000 mg
Lower Respiratory Tract	Mild/Moderate	500 mg	q 12h	1000 mg
	Severe/Complicated*	750 mg	q 12h	1500 mg
Bone & Joint				
Skin & Soft Tissue				
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	q 12h	1000 mg

* e.g. hospital-acquired pneumonia, osteomyelitis.

Depending on the severity of the infections, as well as the clinical and bacteriological responses, the average treatment period should be approximately 7 to 14 days. Generally, treatment should last 3 days beyond the disappearance of clinical symptoms or until cultures are sterile. Patients with osteomyelitis may require treatment for a minimum of 6 to 8 weeks and up to 3 months. With acute cystitis, a five-day treatment may be sufficient.

Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine (see Product Monograph: HUMAN PHARMACOLOGY). This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustment. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

Creatinine Clearance mL/min (mL/s)	Dose
> 30 (0.5)	No dosage adjustment
< 30 (0.5)	Use recommended dose once daily or half the dose twice daily
and patients on hemodialysis or peritoneal dialysis	

When only the serum creatinine concentration is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function:

Males: $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100mL)}}$

Females: 0.85 x the above value

To convert to international units, multiply result by 0.01667

CHILDREN

The safety and efficacy of CIPRO® in children have not been established. CIPRO® should not be used in prepubertal patients (see WARNINGS).

DOSAGE FORMS**Availability**

CIPRO® 250—each tablet contains ciprofloxacin hydrochloride monohydrate equivalent to 250 mg ciprofloxacin.

CIPRO® 500—each tablet contains ciprofloxacin hydrochloride monohydrate equivalent to 500 mg ciprofloxacin.

CIPRO® 750—each tablet contains ciprofloxacin hydrochloride monohydrate equivalent to 750 mg ciprofloxacin.

STORE BELOW 30° C (86° F).

	Strength	Tablet Identification
Bottles of 50	250 mg	Miles 512
	500 mg	Miles 513
	750 mg	Miles 514
Unit Dose Package of 100	500 mg	Miles 513
	750 mg	Miles 514

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