Intravenous Chlorpromazine for the Emergency Treatment of Uncontrolled Symptomatic Hypertension in the Pre-Hospital Setting: Data from 500 consecutive cases

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Abstract

Background: Chlorpromazine is a dopamine-receptor antagonist antipsychotic agent. Because of its strong alpha-blocking and sedative actions, it has also been used as emergency therapy for extreme arterial hypertension. Published reports to date have included very small numbers of patients (i.e., 5–30).

Objectives: To analyze data on almost 500 patients who received intravenous chlorpromazine for the emergency treatment of uncontrolled symptomatic hypertension in the pre-hospital setting.

Methods: We reviewed data from 496 consecutive patients who received intravenous chlorpromazine as emergency therapy for uncontrolled symptomatic hypertension. Chlorpromazine was injected intravenously. The dose was 1 mg every 2–5 minutes until the systolic pressure was ≤140 mmHg and the diastolic pressure ≤100 mmHg with alleviation of symptoms.

Results: The mean dose of chlorpromazine administered was 4.5 ± 5 mg (range 1–50 mg). Only 33 patients (7%) required >10 mg. Chlorpromazine reduced systolic BP from 222.82 ± 26.31 to 164.93 ± 22.66 mmHg ($P < 0.001$) and diastolic BP from 113.5 ± 16.63 to 85.83 ± 11.61 mmHg ($P < 0.001$). The sinus rate decreased from 97.9 ± 23.5 to 92.2 ± 19.7 beats per minute ($P < 0.001$). These results were achieved within the first 37 ± 11 minutes.

Conclusions: Intravenous chlorpromazine is safe and effective when used as emergency treatment for uncontrolled symptomatic hypertension.

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Chlorpromazine is a dopamine-receptor antagonist mainly used as an antipsychotic agent [1]. Because of its strong alpha-blocking and sedative actions, it has also been used as emergency treatment for extreme arterial hypertension. In fact, intravenous chlorpromazine is commonly used for this indication in Scandinavia [2] and Israel [3]. Only a few studies have systematically evaluated the efficacy and safety of chlorpromazine in severe hypertension. All these reports have consistently demonstrated that parenteral chlorpromazine rapidly and steadily decreases both systolic and diastolic high BP [2,4–6]. These studies, however, included very small numbers of patients (i.e., between 5 and 30) [2,4–6]. We report data collected over 15 years on almost 500 patients who received intravenous chlorpromazine as acute therapy for severe uncontrolled symptomatic hypertension.

BP = blood pressure

Patients and Methods

SHL Medical Services, currently serving over 60,000 subscribers, provides emergency medical aid that includes assistance with mobile intensive coronary care units. The SHL system has been previously described in detail elsewhere [7]. Briefly, at the time of subscription to SHL Medical Services, every individual undergoes a medical interview and his/her demographic and medical data are entered into a computerized database. Each time an ambulance is dispatched to a subscriber, the database is updated with the following information: a) the symptoms that prompted the ambulance dispatch; b) the heart rate, blood pressure and main physical findings at the time of arrival, following emergency therapy and as indicated thereafter; c) the final values of heart rate and blood pressure (recorded when the patient arrives to a hospital or when the decision is made to leave the patient at home); d) a description of the electrocardiogram; e) the working diagnosis made by the SHL team's physician; and f) all the medications (including doses and route of administration) given prior to or during transport to a hospital. Finally, the status of all patients who required ambulance dispatch (whether hospitalized or left at home) is ascertained the next day via telephone interview.

The common practice in SHL for the last 15 years has been to use intravenous chlorpromazine for the pre-hospital treatment of severe hypertension, defined as a systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg accompanied by symptoms associated with hypertension, including heart failure and acute neurologic syndromes. Chlorpromazine was given as follows: one 50 mg ampoule of Taroctyl® (Taro Pharmaceutics, Israel) diluted in 50 ml of normal saline and administered intravenously as 1 ml (1 mg) every 2–5 minutes until the therapeutic goal has been achieved. The goal is defined as reduction of the systolic pressure to ≤140 mmHg and reduction of the diastolic pressure to ≤100 mmHg with alleviation of symptoms. According to the discretion of the physician and severity of the hypertension, intravenous chlorpromazine is given as initial therapy (when the blood pres-

sure is very high) or after therapy with other agents (such as sublingual nifedipine or nitroglycerin or intravenous verapamil, furosemide or morphine) has failed to achieve the therapeutic goal.

For this study, we reviewed all the charts of patients who received intravenous chlorpromazine for the treatment of hypertension since the formation of SHL in 1987 until the present. Review of these data collected by SHL was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center.

Results

We identified 496 consecutive patients who received intravenous chlorpromazine for the emergency treatment of uncontrolled symptomatic hypertension [Table 1]. Eighty-nine (18%) of these patients received chlorpromazine as the only antihypertensive therapy, whereas 407 (82%) received chlorpromazine when other medications failed to control the severe hypertension.

The most common symptoms reported at the time of ambulance arrival were shortness of breath (55%), neurologic symptoms (including headache, dizziness, stroke; 16%), and chest pain (11%). The most common working diagnoses were pulmonary edema and heart failure exacerbation (49% of the study patients). General malaise attributed to severe hypertension was the only diagnosis for 176 patients (36%) [Table 1].

Patients treated with additional drugs more commonly had underlying heart failure (52% vs. 30%, $P < 0.001$) [Table 1] and more commonly presented with dyspnea and heart failure exacerbation compared with patients treated exclusively with chlorpromazine (62% vs. 23% for dyspnea, $P < 0.001$, and 57% vs. 11% for signs of heart failure exacerbation, $P < 0.001$). Patients treated only with chlorpromazine were more likely to present with "hypertension" without additional specific signs or symptoms (56% compared with 31%, $P < 0.001$) [Table 1]. Systolic blood pressure was similar in both groups, but diastolic blood pressure was higher in patients receiving additional antihypertensive therapy [Table 1].

The mean dose of intravenous chlorpromazine administered for control of severe blood pressure was 4.51 ± 5 mg (range 1–50 mg, median 3 mg). Only 33 (7%) patients required >10 mg chlorpromazine: these patients were comparable to patients requiring ≤10 mg in terms of gender, age, and underlying heart disease but they had higher values of blood pressure before

Table 1. Demographic and clinical data of all patients who received intravenous chlorpromazine as part of emergency therapy of uncontrolled symptomatic hypertension

Characteristic	All patients	Group I (chlorpromazine only)	Group II (chlorpromazine with other drugs)*	*P*
No. of patients	496	89 (18%)	407 (82%)	
Males (%)	207 (42%)	30 (34%)	177 (44%)	0.098
Age (yrs)	74.7 ± 10.5	73.3 ± 10.9	75 ± 10.4	0.19
Underlying disease				
Hypertension	383 (77%)	69 (78%)	314 (77%)	0.94
Diabetes mellitus	154 (31%)	23 (26%)	131 (32%)	0.26
Heart failure	236 (48%)	26 (30%)	210 (52%)	<0.001
Lung disease	84 (17%)	17 (19%)	67 (17%)	0.54
Renal failure	94 (19%)	11 (12%)	83 (20%)	0.1
Old MI	238 (48%)	35 (40%)	203 (50%)	0.079
History of CABG	111 (22%)	18 (20%)	93 (23%)	0.67
Old stroke	81 (16%)	12 (14%)	69 (17%)	0.53
Paroxysmal AF	126 (25%)	17 (19%)	109 (27%)	0.052
Chronic AF	44 (9%)	4 (5%)	40 (10%)	0.67
Main complaint				<0.001
Chest pain	55 (11%)	7 (8%)	48 (12%)	
Dyspnea	272 (55%)	20 (23%)	252 (62%)	
Neurologic	77 (16%)	26 (29%)	51 (13%)	
Non-specific	90 (18%)	36 (40%)	54 (13%)	
Working diagnosis				<0.001
Hypertension	176 (36%)	50 (56%)	126 (31%)	
Pulmonary edema	240 (49%)	10 (11%)	230 (57%)	
Unstable angina	15 (3%)	1 (1%)	14 (3%)	
Cerebrovascular event	16 (3%)	10 (11%)	6 (2%)	
Other	48 (9%)	18 (20%)	30 (7%)	
Pretreatment BP				
Systolic	222.51 ± 26.31	221.52 ± 26.22	222.72 ± 26.37	0.7
Diastolic	113.47 ± 16.6	109.61 ± 16.05	114.32 ± 16.62	0.015

* Additional medications included one or more of the following: intravenous furosemide (130 ± 60 mg), morphine (5.4 ± 2.6 mg), verapamil (5 ± 3.3 mg) and/or sublingual nitroglycerin (5.8 ± 3 mg) or nifedipine (10.9 ± 3.7 mg).
MI = myocardial infarction, AF = atrial fibrillation, CABG = coronary artery bypass graft surgery.

Table 2. Demographic and clinical data of patients who received "low" dose versus "high" dose intravenous chlorpromazine

Characteristic	All patients	Group I (Chlorpromazine dose ≤10 mg)	Group II (Chlorpromazine dose >10 mg)	*P*
No. of patients	496	463 (93%)	33 (7%)	
Males (%)	207 (42%)	193 (42%)	14 (42%)	0.93
Age	74.7 ± 10.5	74.6 ± 10.6	75.4 ± 8.6	0.66
Underlying disease				
Hypertension	383 (77%)	356 (77%)	27 (82%)	0.67
Diabetes mellitus	154 (31%)	141 (31%)	13 (39%)	0.33
Heart failure	236 (48%)	218 (47%)	18 (55%)	0.47
Old MI	238 (48%)	221 (48%)	17 (52%)	0.72
History of CABG	111 (22%)	103 (22%)	8 (24%)	0.83
Old stroke	81 (16%)	74 (16%)	7 (21%)	0.46
Main complaint				0.98
Chest pain	55 (11%)	52 (11%)	3 (9%)	
Dyspnea	272 (55%)	253 (55%)	19 (58%)	
Neurologic	77 (16%)	72 (16%)	5 (15%)	
Non-specific	90 (18%)	84 (18%)	6 (18%)	
Working diagnosis				0.88
Hypertension	176 (36%)	164 (36%)	12 (36%)	
Pulmonary edema	240 (49%)	223 (48%)	17 (52%)	
Unstable angina	15 (3%)	15 (100%)		
Cerebrovascular event	16 (3%)	15 (3%)	1 (3%)	
Pretreatment BP				
Systolic	222.51 ± 26.31	220.6 ± 25.12	249.39 ± 28.28	<0.001
Diastolic	113.47 ± 16.6	113.02 ± 16.27	119.76 ± 19.96	0.024

therapy [Table 2]. Patients for whom chlorpromazine was the only antihypertensive medication received 5.18 ± 5.26 mg (range 1–30 mg), a dose significantly higher than that received by patients who were also treated by other drugs (mean dose 4.36 ± 4.92 mg, range 1–50 mg, $P = 0.011$).

Intravenous chlorpromazine reduced the systolic BP from an initial value of 222.82 ± 26.31 mmHg to a final value of 164.93 ± 22.66 mmHg ($P < 0.001$). Similarly, the diastolic BP was lowered with chlorpromazine from 113.5 ± 16.63 to 85.83 ± 11.61 mmHg ($P < 0.001$). The resolution of hypertension was accompanied by a reduction in heart rate as follows: 405 patients (82%) were in sinus rhythm when chlorpromazine was administered for severe hypertension and their heart rate was lowered from 97.9 ± 23.5 to 92.2 ± 19.7 beats/min ($P < 0.001$). Sixty-three patients (12.7%) were in atrial fibrillation and their ventricular rate was lowered from 120.9 ± 26.7 to 103.9 ± 22 beats/min ($P < 0.001$). These results were achieved within the 37 ± 11 minutes that the ambulance team spent with the patients (estimated from the time of arrival to the patients' home to the time of arrival to the emergency room). The QT interval was not measured systematically throughout the treatment, but no episodes of torsade de points were documented.

Following initial therapy, 127 patients (26%) remained at home and 368 (74%) were transported to the hospital. The vital status was ascertained for all patients the next day. All the patients who remained at home were alive, whereas 3 (0.82%) of those who were transported to the hospital died within 24 hours. Thus, the short-term mortality for the whole study cohort was 0.7%. None of the deaths was directly ascribed to the antihypertensive therapy, and no serious side effects were reported by the medical team.

Discussion

Our findings show that intravenous chlorpromazine is highly effective in the emergency treatment of severe uncontrolled symptomatic hypertension. With 496 consecutive patients included in our study, this is, by far, the largest study on the use of chlorpromazine for the emergency treatment of severe hypertension. Indeed, the number of patients in our study is 10 times larger than the number in all previous studies combined [2,4–6,8].

Our study population is representative of individuals suffering from hypertensive crisis in terms of age, gender and underlying heart disease [2,4–6,8]. In addition, the initial values of systolic and diastolic BP were comparable to those recorded in patients participating in similar trials [2,4–6,8]. Moreover, the results obtained with intravenous chlorpromazine were remarkable: by the time the patients arrived at the emergency room (within 37 ± 11 minutes), only 35% of them still had a systolic BP >170 mmHg and only 10% had systolic BP levels ≥ 200 mmHg. Similarly, only 23% and 5% of patients had diastolic BP >100 and ≥ 110 mmHg, respectively, by the time of arrival to the emergency room.

The efficacy and safety of chlorpromazine observed in our series are especially noteworthy because the majority of our patients had a history of heart disease, cardiac symptoms and/or evidence of heart failure. Indeed, chlorpromazine might be particularly suitable for the emergency treatment of severe hypertension in cardiac patients for two reasons. Firstly, previous work from our institution [3] suggests that intravenous administration of chlorpromazine in patients with left ventricular failure is followed by a significant reduction in systemic vascular resistance and pulmonary capillary wedge pressure – with a concomitant increase in cardiac output – without increasing the heart rate and oxygen consumption. Secondly, intravenous chlorpromazine has strong sedative effects that contribute to blood pressure reduction in patients with emotional stress secondary to cardiac symptoms.

An outstanding finding of this study was the complete absence of serious adverse effects. This is precisely one of the reasons we are keen to share our findings with our colleagues. It must be noted, however, that the time frame during which the drug was administered was short and that any adverse effects that might have resulted from a longer period of drug administration (hours, days) did not have time to develop.

The very large number of patients in our series (almost 500 patients) and the <1% mortality rate that was recorded suggest that intravenous chlorpromazine is, at the very least, a safe drug. Our large study also suggests that chlorpromazine is very effective in acutely reducing high blood pressure. Nevertheless, the role of chlorpromazine in the emergency treatment of severe hypertension can only be established with controlled studies. It should be noted, however, that one such controlled study [2] – albeit with only 24 patients treated with chlorpromazine – has already been conducted. In that study, intravenous chlorpromazine was as effective in reducing severe hypertension as intravenous diazoxide or dihydralazine (considered by many as first-line drugs).

Finally, a word of caution. Because hypertensive crisis may be associated with confusional state and given that chlorpromazine potentially may add to that state and cause some confusion of the clinical situation, physicians should exert caution when deciding to use chlorpromazine for a patient who is not fully alert.

Study limitations

Although the strength of this study lies in its size, it suffers from some weaknesses related to its being a retrospective observational investigation. There is no control group for comparison, and the decision to use the drug was not randomized. Mortality data are available only for the first 24 hours.

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