Received: 15 May 2022 | **Accepted:** 08 Nov 2022
DOI: 10.54005/geneltip.1116922

ORIGINAL ARTICLE

The Acute Effect of Chlorpromazine on Body Temperature in Intensive Care Unit Patients

Klorpromazinin Yoğun Bakım Hastalarının Vücut Sıcaklığı Üzerindeki Akut Etkisi

[1]Omur Ilban, [1]Muhammet Emin Zora, [2]Bulent Devrim Akcay, [1]Jale Bengi Celik, [1]Faruk Cicekci, [1]Mehmet Ali Bas, [1]Ates Duman

[1]Department of Anesthesiology, Selcuk University Medical Faculty, Konya, Turkey.
[2]Department of Mental Health and Disease, University of Health Sciences, Gulhane School of Medicine, Ankara,Turkey.

Correspondence

Omur Ilban, Selçuk Üniversitesi Tıp Fakultesi, Alaaddin Keykubat Yerleşkesi, Postal code: 42130, Selçuklu - Konya/ Türkiye

E-Mail: droilban@gmail,com

How to cite ?

İlban Ö. , Zora M. E. , Akçay B. D. , Çelik J. B. , Çiçekci F. , Baş M. A. , Duman A. The Acute Effect of Chlorpromazine on Body Temperature in Intensive Care Unit Patients. Genel Tıp Dergisi. 2022; 32(6): 658-665.

ABSTRACT

Aim: Hypothermia is a rare but serious complication of antipsychotic drugs that can result in death. In this study, we aimed to investigate body temperature alterations in acute phase of chlorpromazine treatment, the relationship of inflammatory indicators and risk factors for hypothermic effect on intensive care unit (ICU) patients.
Materials and methods: 63 intensive care patients who needed sedative treatment due to agitation were divided into two groups as Group 1 (n = 30) with temperatures ≤ 38°C, and Group 2 (n = 33) with temperatures > 38°C according to baseline body temperatures. Also, recurrent measurements for 12 hours were made at specific intervals following 25 mg intravenous chlorpromazine.
Results: In Group 1, decrease in body temperatures was significant from 4th to 12th hours ($p < 0.01$), while in Group 2, significant decreases in body temperatures at all measurement hours were observed ($p < 0.01$). Temperature changes (delta temperature) observed at specific measurement intervals were significantly higher in Group 2 compared to Group 1. That difference was statistically significant at all intervals except for ΔTemperature B-6 ($p < 0.05$). The odds of hypothermic effects by chlorpromazine were 16%, 46%, 3%, and 18% for Acute Physiology and Chronic Health Evaluation II, procalcitonin, C-reactive protein, and white blood cells, respectively.
Conclusion: Chlorpromazine treatment applied for agitation in ICU patients was associated with acute hypothermic effect. Severity of disease and comorbidities might increase risk of hypothermia, and inflammatory biomarkers might be predictors of adverse drug reaction.

Keywords: adverse drug reaction; body temperature changes; chlorpromazine; intensive care unit; psychomotor agitation

ÖZ

Amaç: Hipotermi, antipsikotik ilaçların ölümle sonuçlanabilen nadir fakat ciddi bir komplikasyonudur. Bu çalışmada, yoğun bakım ünitesindeki (YBÜ) hastalara uygulanan klorpromazin tedavisinin akut fazındaki vücut sıcaklık değişimlerini, inflamatuar göstergeler ile ilişkisini ve hipotermik etki için risk faktörlerini araştırmayı amaçladık.
Materyal ve metod: Ajitasyon nedeniyle sedatif tedaviye ihtiyaç duyan 63 yoğun bakım hastası, bazal vücut sıcaklıklarına göre Grup 1 (n = 30; ≤ 38°C) ve Grup 2 (n = 33; > 38°C) olarak iki gruba ayrıldı. Aynı zamanda, 25 mg intravenöz klorpromazini takiben 12 saat süreyle belirli aralıklarla tekrarlayan ölçümler yapıldı.
Bulgular: Grup 1'de 4. saatten 12. saate kadar olan vücut sıcaklıklarında anlamlı azalma görülürken ($p < 0.01$), Grup 2'deki vücut sıcaklıklarında tüm ölçüm saatlerinde belirgin azalma gözlendi ($p < 0.01$). Grup 1 ile karşılaştırıldığında, belirli ölçüm aralıklarında gözlenen sıcaklık değişiklikleri Grup 2'de önemli ölçüde yüksekti. Bu fark, ΔSıcaklık B-6 hariç tüm aralıklarda istatistiksel olarak anlamlıydı ($p < 0.05$). Klorpromazin tedavisi ile hipotermik etki olasılığı Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi II, prokalsitonin, C-reaktif protein ve beyaz kan hücreleri için sırasıyla %16, %46, %3 ve %18 olarak bulundu.
Sonuç: Yoğun bakım hastalarında ajitasyon için uygulanan klorpromazin tedavisi akut hipotermik etki ile ilişkilidir. Hastalık şiddeti ve komorbiditeler hipotermi riskini artırabilir ve inflamatuar biyomarkırlar olumsuz ilaç reaksiyonunun göstergeleri olabilir.

Anahtar kelimeler: olumsuz ilaç reaksiyonu; vücut sıcaklık değişimleri; klorpromazin; yoğun bakım ünitesi; psikomotor ajitasyon

Introduction

If the heat loss in the body is greater than the amount of heat produced, hypothermia occurs, which is defined by a core body temperature below 35°C. The clinical picture of hypothermic patients worsens significantly with the decrease in body temperature. Hypothermia may induce deterioration in pharmacodynamics, coagulation disorder, transfusion requirements, impaired coordination, lethargy, delirium, coma, bradycardia, and ventricular fibrillation (1-3). Furthermore, hypothermia is associated with increased ICU mortality in various critically ill patient groups (4).

Antipsychotic drugs (ADs) have the potential to cause hypothermia by affecting the thermoregulatory centre of the hypothalamus. In fact, before ascertaining their antipsychotic activities, the hypothermic effect of ADs had been discovered. For instance, chlorpromazine, haloperidol, and reserpine had been demonstrated to cause moderate hypothermia in mice and rats (5-7). A report yielding the hypothermic effect of chlorpromazine in human beings has also been presented (8). The well-known antipsychotic drug (AD), chlorpromazine, is a derivative of phenothiazine and has been used in psychiatry to control psychoses like schizophrenia and mania. Tranquillizing, anxiolytic, antiemetic, peripheral vasodilator, and hiccup repressor activities of chlorpromazine have also been utilised (9). Its usage during general anaesthesia for suppressing compensatory responses of the body to the cooling process (artificial hibernation) was also reported in 1952 (10). Undesirable and adverse effects of chlorpromazine include hypotension, extrapyramidal abnormalities, endocrine disorders, and sexual dysfunction (9).

Agitation and delirium are encountered in approximately 57% of patients in the intensive care unit (ICU) (11). Self-extubation (12), self-removal of drains/catheters (for example, arterial, venous, urinary, nasogastric), increased systemic/myocardial oxygen consumption, low treatment compliance, self-lacerations, self-fractures, and patient-ventilator mismatch are frequent outcomes in both conditions unless sedation is employed. Also, it has positive end-results in ICU, such as decreased duration of mechanical ventilation (MV) and ICU stay (13).

There are several potential causes of increased agitation (pain, anxiety, withdrawal syndromes, infection, etc.) in ICU. A definite reason for agitation is uncommon but reversible conditions should be recognised and treated. Measures as frequent reorientation, minimal sleep disturbance, night light, and visible clock/calendar may reduce the emergence of agitation (14). However, these methods may not be sufficient to reduce or control the symptoms of agitation after it has already occurred. Methods of physical restriction for agitated patients are frequently used but may have dangerous consequences (15). Therefore, the use of anaesthetics, benzodiazepines, opioid analgesics, phenothiazines, butyrophenones, or neuromuscular blockers supporting these methods is advised.

Considering the potential effects of antipsychotic drugs on body temperature, we hypothesized that a single dose of chlorpromazine therapy causes an acute hypothermic effect in critically ill patients. To trial this hypothesis, we investigated the body temperatures of the patients for 12 hours after the administration of 25 mg IV chlorpromazine for agitation, along with the relationship of inflammatory indicators and potential risk factors for the development of adverse drug reaction (ADR).

Materials and Methods

A total of 63 patients were included in this observational study of prospective character; between June 2018 and July 2019, the patients were consecutively admitted to the Anesthesiology and Reanimation ICU at Selcuk University and received single-dose chlorpromazine. The study was conducted according to the guidelines stated by the Declaration of Helsinki and the Ethics Committee of Selcuk University Medical School (no: 2016/4); it was also included in the Australian New Zealand Clinical Trial Registry (ACTRN12621000700831). In addition, informed consent of the patients or their relatives were obtained.

According to baseline body temperatures, two groups were defined, 30 patients presenting temperatures ≤ 38°C as Group 1, and 33 patients exhibiting temperatures > 38°C as Group 2. Body temperature > 38°C was defined as high fever (16).

Patients aged ≥ 18 years and staying in the ICU for at least 24 hours after admission were included in the study. Schizophrenia, hyperthermia syndromes (for example, malignant hyperthermia, neuroleptic malignant syndrome), endocrinal states which may cause hyperthermia, shock states (with lactic acid levels > 4 mmol), diagnosed hepatitis (with alanine aminotransferase levels higher than twice the upper limit), chronic hepatic insufficiency, pregnancy, breastfeeding, use of medications (such as antibiotics, steroids, non-steroid anti-inflammatory drugs, antipyretics, sedative-hypnotics, and anticonvulsants), and a history of blood product transfusion or receiving general anesthesia within 24 hours were the exclusion criteria.

For treating agitation, 25 mg single dose chlorpromazine was applied intravenously with (IV) slow infusion within 30 minutes. Body temperatures for both groups were measured once by digital thermometer at 0th, 1st, 2nd, 4th, 6th, 8th, 10th, and 12th hours of the treatment. In order to obtain a closer value to the temperature of the hypothalamic thermoregulatory centre, non-invasive measurements were made at the tympanic membrane. The ADR was considered clinically significant when a decrease of 0.5°C in body temperature was detected during the 12 hours following chlorpromazine administration (17).

Agitation status was assessed by Richmond Agitation and Sedation Scale (RASS). Patients with a RASS score ≥2 were included in the study (18). Since distress behaviours such as irritability, agitation, and restlessness may be associated with pain, cooperative patients were evaluated with the Numerical Rating Scale (NRS) and the Visual Analogue Scale (VAS). NRS and VAS scores ≥1 meant the exclusion from the study (19). The pain status of unconscious patients was evaluated by the Behavioural Pain Scale (BPS). Patients with BPS score ≥4 were also excluded (20).

Sociodemographic data, renal, pulmonary, cardiovascular disorders, diabetes mellitus, surgery, trauma, mechanical ventilation, and vasopressor need were analysed. The disease severity was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE II) and the Simplified Acute Physiology Score (SAPS II). Serum biomarkers related with systemic inflammation and pyrexia such as white blood cells (WBC), C-reactive protein (CRP), and procalcitonin (PCT) levels were measured. Clinical outcomes, including length of the ICU stay and 28-day ICU mortality were also registered. The role of chlorpromazine in the hypothermic effect was evaluated by ADR Probability Scale, also known as Naranjo Probability Scale (21). Body temperature alterations and the relationship of inflammatory biomarkers with ADR development were the primary outcome measures, efficacy and safety of chlorpromazine application were the secondary outcome measures.

Sample size calculation

In order to define the minimum sample size, a power analysis was performed by an Independent Samples t-test, using the publicly available statistical software G*Power, version 3.1. Before the start of the study, there was no published information about the effect of chlorpromazine on body temperature; as such, a sample size estimation based on previous studies was not possible. Therefore, we first conducted a pilot study on 20 patients with the same methods as those of the main study. In our preliminary study, the mean body temperature at baseline was 37.6 °C (SD 0.65). In order to detect a significant difference in body temperature of 0.5°C during the 12 hour period (17), a power analysis was carried out using a 2-sided confidence level of 95% ($p < 0.05$), an effect size of 77% and a power of 80%. After considering the 10% dropout rate, the sample size was defined as at least 62 patients.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 20 (SPSS Inc., Chicago, IL, USA). Proportions were used to describe categorical variables while means with standard deviation for continuous variables. The former variables were compared by the Chi-squared or Fisher's exact tests. The Shapiro-Wilk test analysed the distribution normality of continuous variables. The Independent-Samples t-test was used to analyse the statistical differences among the means of normally distributed populations. The nonparametric Mann-Whitney U test analysed abnormal distributions. Comparison of the body temperature alterations of the patients of groups 1 and 2 was performed by the repeated measures analysis of variance (rANOVA). The Pearson's correlation coefficient was used for assessing the correlations (r values). Risk factors for developing hypothermic effect independently associated with the treatment of chlorpromazine were evaluated by a logistic regression model. At first, the outcome (ADR) was taken into account as the dependent variable, and age, gender, comorbid conditions, cause of admission to the ICU, APACHE II score, SAPS II score, RASS score, creatinine, WBC, CRP, PCT, mechanical ventilation, and use of vasopressors were assumed as independent variables. Those showing univariately a significant result ($p < 0.2$) were submitted to the corresponding multivariate logistic regression. The final model for ADR included the following covariates: diabetes mellitus, APACHE II score, SAPS II score, PCT, CRP, WBC, and use of vasopressors. The receiver operating characteristic (ROC) curve was used to analyse the predictive capacity of inflammatory biomarkers in differentiating the ADR. The area under the curve (AUC) and a confidence interval (CI) of 95% were recorded. The determination of adequate discriminatory cut-off values was done by calculating the Youden's indices (sensitivity + specificity – 1). All tests of significance were two-tailed with a p-value < 0.05.

Results

Of 245 critically ill patients, 116 (47.3%) were diagnosed with psychomotor agitation. Patients with RASS < 2 (n = 39), no informed consent (n = 3), antibiotic treatment (n = 3), lactate levels > 4 mmol/L (n = 2), schizophrenia diagnosis (n = 2), recipients of blood product transfusions (n = 2), younger than 18 years old (n = 1), and died within 24 hours after inclusion (n = 1) were excluded from the study. The final analysis was performed on 63 patients treated with a single dose of chlorpromazine. There was no difference in age or gender ratio between Group 1 and Group 2 (age, $p = 0.54$; gender, $p = 0.92$). Cardiovascular disease was the most common underlying systemic disease, occurring in 32% of the patients. As specified in Table 1, significant differences were found between groups concerning disease severity, evaluated by APACHE II and SAPS II ($p < 0.01$). Compared to Group 1, the mean values of biomarkers associated with inflammatory response were higher in Group 2, and the increase in PCT levels was statistically significant ($p < 0.01$). Group 1 presented an ADR of 30%, while Group 2, 58% ($p = 0.03$). No statistical difference between groups was observed for other characteristics (Table 1).

The relationship between single dose chlorpromazine and body temperature changes was evaluated. In Group 1, compared to baseline measurements, body temperatures decreased at 1st and 2nd hours, but the variation was not considered statistically significant ($p = 0.23$, and $p = 0.06$, respectively). However, body temperatures measured from the 4th to 12th hour were significantly lower ($p < 0.01$). In Group 2, decreases in body temperatures at all measurements were statistically significant ($p < 0.01$) (Table 2).

The decrease in body temperatures relative to baseline measurements after chlorpromazine dose were analysed by intergroup comparisons. Temperature changes (delta temperature) observed at specific measurement intervals were significantly higher in Group 2. That difference was statistically meaningful

at all intervals except for ΔTemperature B-6 ($p < 0.05$) (Table 3).

Correlation analysis was used to calculate the relationship of PCT with APACHE II and SAPS II scores. In Group 1, PCT was poorly correlated with the scores of APACHE II and SAPS II ($r = 0.273$, $p = 0.14$, and $r = 0.215$, $p = 0.25$, respectively), while a significant positive correlation was detected in Group 2 ($r = 0.371$, $p = 0.03$, and $r = 0.352$, $p = 0.04$, respectively).

For assessing the potential risk factors for the development of ADR, patients were divided into 2 groups, one with ADR (28 patients), and one with no ADR (35 patients). The odds of hypothermic effects by chlorpromazine treatment was 16%, 46%, 3%, and 18% for APACHE II (Odds Ratio, OR: 1.16 [95% CI: 1.021-1.373], $p = 0.024$), PCT (OR: 1.46 [95% CI: 1.125-1.905], $p = 0.005$), CRP (OR: 1.03 [95% CI: 1.006-1.045], $p = 0.009$), and WBC (OR: 1.18 [95% CI: 1.019-1.359], $p = 0.027$), respectively (Figure 1).

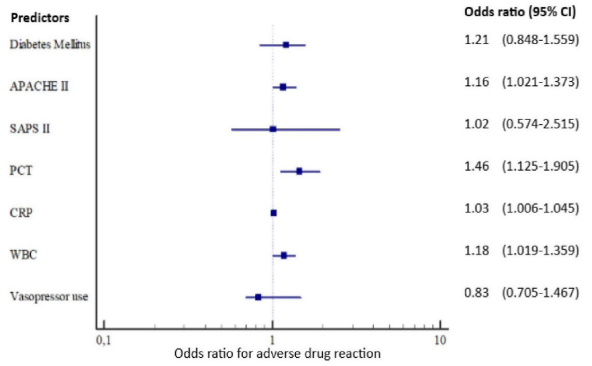

Figure 1. Risk factors for hypothermic effect with the treatment of chlorpromazine. CI: confidence interval. Other abbreviations – see Table 1

Since PCT, CRP, and WBC levels have been verified to display a significant relation with inflammatory states and disease severity, the inflammatory biomarker levels of patients treated with chlorpromazine were analysed with ROC curves as a predictive ADR indicator. The ROC curves were calculated based on all the results, minding the clinical significance of body temperature changes over 12 hours after chlorpromazine treatment. The ROC curves for PCT, CRP, and WBC are shown in Figure 2.

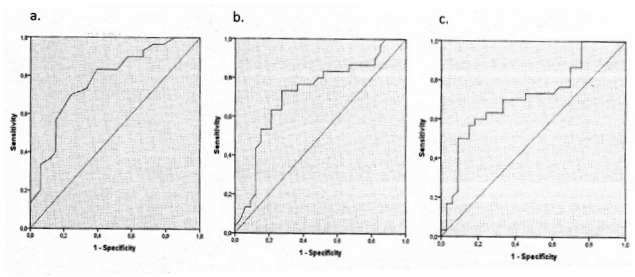

Figure 2. Receiver operating characteristic (ROC) curves for a) procalcitonin, b) C-reactive protein, c) white blood cells to predict hypothermic effect.

Table 1. Baseline characteristics of patients

Variables	All patients (n = 63)	Group 1 (n = 30)	Group 2 (n = 33)	p value
Age in years	58.7 ± 19.1	57.2 ± 21.3	60.1 ± 17	0.54
Gender, male, n (%)	34 (54)	16 (53)	18 (55)	0.92
Comorbid condition, n (%)				
Renal diseases	18 (29)	8 (27)	10 (30)	0.75
Pulmonary diseases	14 (22)	7 (23)	7 (21)	0.84
Cardiovascular diseases	20 (32)	10 (33)	10 (30)	0.8
Diabetes mellitus	18 (29)	8 (27)	10 (30)	0.75
Surgery/trauma	13 (21)	6 (20)	7 (21)	0.91
APACHE II	23.6 ± 4.3	22.1 ± 3.5	25 ± 4.6	**<0.01**
SAPS II	39.6 ± 5	37 ± 4.7	42.1 ± 3.9	**0.01**
RASS	2.79 ± 0.7	2.76 ± 0.8	2.81 ± 0.7	0.8
Serum creatinine (mg/dL)	0.95 ± 0.4	0.91 ± 0.4	1 ± 0.4	0.35
WBC (×10³/μL)	11.5 ± 5.3	10.5 ± 4.5	12.4 ± 5.8	0.15
CRP (mg/L)	88.8 ± 37.2	84.1 ± 35.4	93.1 ± 38.9	0.36
Procalcitonin (μg/L)	3.6 ± 4.6	2.1 ± 4.1	5 ± 4.6	**<0.01**
ADR	28 (44)	9 (30)	19 (58)	**0.03**
Mechanical ventilation, n (%)	42 (67)	19 (63)	23 (70)	0.59
Vasopressor use, n (%)	30 (48)	14 (47)	16 (49)	0.89
ICU length of stay (days)	19.2 ± 9.7	18.1 ± 9.1	20.2 ± 10.3	0.42
28-day ICU mortality, n (%)	31 (49)	14 (47)	17 (52)	0.7

Data was shown as mean ± standard deviation or n (%)

APACHE II: Acute Physiological and Chronic Health Evaluation, SAPS II: Simplified Acute Physiology Score, RASS: Richmond Agitation and Sedation Scale, WBC: white blood cells, CRP: C-reactive protein, ADR: adverse drug reaction, ICU: Intensive Care Unit

Table 2. Comparison of intra-group body temperature measurements

Measurements (°C)	Group 1 (n = 30)	p value	Group 2 (n = 33)	p value
Baseline	37.20 ± 0.54		38.61 ± 0.52	
1st hour	37.18 ± 0.53	0.23	38.51 ± 0.53	**< 0.01**
2nd hour	37.17 ± 0.53	0.06	38.40 ± 0.52	**< 0.01**
4th hour	37.01 ± 0.54	**< 0.01**	38.30 ± 0.53	**< 0.01**
6th hour	36.91 ± 0.51	**< 0.01**	38.21 ± 0.57	**< 0.01**
8th hour	36.83 ± 0,50	**< 0.01**	38.12 ± 0.54	**< 0.01**
10th hour	36.94 ± 0.51	**< 0.01**	38.02 ± 0.56	**< 0.01**
12th hour	36.97 ± 0.50	**< 0.01**	38.04 ± 0.57	**< 0.01**

Data was shown as mean ± standard deviation. Baseline vs other intra-group measurements

Table 3. Comparison of body temperature changes after chlorpromazine treatment

Variables (°C)	Group 1 (n = 30)	Group 2 (n = 33)	p value
Δ-Temperature $_{B-1}$	- 0.04 ± 0.2	- 0.26 ± 0.2	**< 0.01**
Δ-Temperature $_{B-2}$	- 0.06 ± 0.2	- 0.51 ± 0.1	**< 0.01**
Δ-Temperature $_{B-4}$	- 0.51 ± 0.5	- 0.76 ± 0.3	**0.01**
Δ-Temperature $_{B-6}$	- 0.78 ± 0.5	- 0.99 ± 0.4	0.05
Δ-Temperature $_{B-8}$	- 0.98 ± 0.5	- 1.24 ± 0.3	**0.02**
Δ-Temperature $_{B-10}$	- 0.69 ± 0.5	- 1.50 ± 0.4	**< 0.01**
Δ-Temperature $_{B-12}$	- 0.62 ± 0.5	- 1.44 ± 0.5	**< 0.01**

Data shown as mean ± standard deviation.

ΔTemperature B-1, the difference between baseline and hour 1 temperature; ΔTemperature B-2, the difference between baseline and hour 2 temperature; ΔTemperature B-4, the difference between baseline and hour 4 temperature; ΔTemperature B-6, the difference between baseline and hour 6 temperature; ΔTemperature B-8, the difference between baseline and hour 8 temperature; ΔTemperature B-10, the difference between baseline and hour 10 temperature; ΔTemperature B-12, the difference between baseline and hour 12 temperature.

The most specific parameter was the WBC (81.8%) with 12.8 103/μL cut-off value (AUC: 0.714 [95%CI: 0.584–0.844], p = 0.004), but concurrently it performed the lowest diagnostic sensitivity (60%). PCT was more sensitive (70%) with 2.75 μg/L cut-off value (AUC: 0.776 [95%CI: 0.661–0.891], p < 0.001) but less specific (75.8%) than WBC. In our study group CRP was characterized by the highest diagnostic sensitivity (73.3%) with 89 mg/L cut-off value (AUC: 0.719 [95%CI: 0.589–0.850], p = 0.003) but the lowest diagnostic specificity (72.7%) (Table 4).

Comparison of the AUC for PCT, CRP, and WBC revealed no meaningful difference, so it was possible to assume that the inflammatory biomarkers present resembling diagnostic value for risk assessment of ADR development in the ICU. Table 4 records the AUC comparison data along with the ROC curves describing parameters.

The effect of single-dose chlorpromazine administration on the emergence of hypothermic effect was assessed by the Naranjo Probability Scale. The total score was calculated as +7, and ADR was considered probable.

Discussion

This study investigated body temperature alterations in the acute phase of chlorpromazine treatment and whether the inflammatory response was different in patients with altered body temperatures. Also, the risk factors for ADR were analysed. Under normal room temperatures, we have found that 25 mg chlorpromazine applied for the treatment of agitation in ICU had the potential for an early onset of the hypothermic effect. Severity scores and inflammatory biomarkers had clinical value to predict chlorpromazine induced ADR.

Hypothermia might be a serious complication. It has been reported that unexplained deaths during the treatment might be related to AD induced hypothermia (22). Chlorpromazine is a phenothiazine derivative neuroleptic and commonly preferred in neuropsychiatry, anesthesiology, and surgery due to its sedative, antiemetic, and vagolytic effects (23). The mechanism of how ADs affect the thermoregulatory centre in human beings has not been fully understood. ADs may cause hypothermia with different mechanisms. For instance, ADs have a stronger affinity for 5-HT2A receptors than dopamine (D2) receptors, and serotonin interferes with thermoregulation. Another mechanism is the blockade of alpha-2 adrenergic receptors by ADs (for example, chlorpromazine, risperidone, clozapine, and thioridazine). On this wise, they inhibit the peripheral responses against heat loss, as vasoconstriction and tremor. Although their mechanisms of action differ, both typical and atypical ADs have been reported to cause hypothermia (24).

Under general anaesthesia, the body cannot compensate for hypothermia since anaesthetic agents inhibit the thermoregulatory centre (25). Nearly all general anaesthetics are eliminated from the body in the first 24 hours after application (23). Since patients underwent surgery in the last 24 hours were not included, body temperature changes may be an appropriate marker for evaluating the agitation developing ADR in surgical ICU patients.

In patients with schizophrenia receiving ADs, body temperatures have been shown to decrease (26). The alteration of thermoregulation in these patients can be explained by the fluctuation of neurotensin

Table 4. Predictive value of serum levels of inflammatory biomarkers

Parameter	Cut-off	Sensitivity	Specificity	PPV	NPV	LR +	LR -	AUC	p
PCT(μg/L)	2.75	70	75.8	72.4	73.5	2.89	0.4	0.776	
CRP(mg/L)	89	73.3	72.7	70.9	75	2.69	0.37	0.719	0.5
WBC($\times 10^3$/μL)	12.8	60	81.8	75	69.2	3.3	0.49	0.714	0.42

Receiver operating characteristic (ROC) plot analysis of laboratory parameters with respect to prediction of hypothermic effect. The p values correspond to the difference between the AUC of the parameters and the AUC of PCT.

Data are presented as %, unless otherwise stated. AUC: area under the receiver-operating-characteristic curve; PPV:positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio. Other abbreviations – see Table 1

levels, one of the most important thermoregulatory peptides. In patients with psychosis, the concentration of neurotensin in the cerebrospinal fluid decreases; however, it turns normal after antipsychotic medication (27). In some reported cases, the risk of AD-induced hypothermia in patients with psychosis was higher than in patients with bipolar disorder or dementia (8). Since the results of patients with psychosis point to the thermoregulatory dysfunction independent of AD treatment (26), patients with schizophrenia were excluded from the study due to their potential thermoregulatory dysfunction causing susceptibility to hypothermia.

There is no direct relationship between a particular antipsychotic dose and hypothermic side effect. The risk is higher in the first 7-day period of the treatment or the case of dose increment, especially in the presence of additional predisposing factors (8,28). In our study, the mild hypothermic effects of single-dose chlorpromazine were observed in the 12-hour follow-up, and no other ADR was encountered. In human beings, hypothermia is accepted to occur when body temperature gets below 35°C (22). Since our patients did not achieve body temperatures below 35°C, which was considered the hypothermia threshold, signs of mild hypothermia (for example, heavy shivering, cold diuresis, cold/white skin) were not observed (29). In addition, the treatment protocol was well tolerated, and no major side effects requiring treatment cessation were observed.

In our study, significant differences in body temperatures were observed in intra- and inter-group comparisons after chlorpromazine administration. When intra-group measurements were analysed, unlike in Group 1, the temperatures at all measurement intervals in Group 2 decreased significantly compared to baseline values. Moreover, the differences observed in the measured values over time were greater in Group 2. In addition, Group 2 patients have higher ADR than Group 1 patients. That suggests that the hypothermic effect is more pronounced in patients presenting high fever.

Adverse drug reaction is defined as a harmful and undesirable response to a medication used in the normal dose range for prophylaxis, diagnosis, treatment, or modification of a physiological function. In order to standardise the assessment of causality for all the adverse drug reactions (ADRs), the Naranjo ADR Probability Scale was developed. In our study, the total score was calculated as +7, and ADR was considered probable. Therefore, significant changes in body temperature after chlorpromazine treatment can be considered as AD induced hypothermic effect.

Severe somatic comorbidities may increase the risk of AD induced hypothermia (22). To define the severity of the disease, broadly used scoring systems are APACHE II and SAPS II. Hale et al. (30) have examined ADRs in ICU patients receiving ADs for treating delirium. APACHE II scores were found considerably higher in the ADR group than in the non-ADR group, so it was noted that the degree of critical disease might have affected the development of ADRs. Compatible with the previous studies, in Group 2, the hypothermic outcome was more prominent since APACHE II and SAPS II values were significantly higher. Also, in our study, the APACHE II score was an independent factor for ADR.

It has been reported that accompanying infections might impair thermal homeostasis (8). WBC and CRP are widely used inflammatory biomarkers in the diagnosis of acute inflammatory states (31). For diagnosing bacterial infections, PCT is considered a better biomarker than CRP; it is also better correlated to the severity (32). In our study, WBC and CRP levels were non-significantly different, while PCT levels were meaningfully higher in Group 2 than Group 1. Parallel to the increase in PCT values, the hypothermic effect of chlorpromazine was more pronounced in Group 2, probably due to the thermal homeostatic disturbance in infected patients. Similarly, the significant correlation between PCT levels and the disease severity in Group 2 suggests that the grade of critical disease is aggravated by the infectious process, facilitating the ADR development.

In the present study, the predictive ability of inflammatory biomarkers in chlorpromazine induced hypothermic effect was analysed. Serum PCT had the largest AUC (0.776), while serum CRP obtained the highest sensitivity (73.3%), and serum WBC had the highest specificity (81.8%). At the same time, the AUC for PCT, CRP, and WBC showed fair discriminative capacity in ADRs (< 0.8), and the predictive accuracy of these biomarkers was analogous ($p > 0.05$). Therefore, inflammatory parameters might present similar predictive value in the assessment of the risk of the hypothermic effect in patients receiving chlorpromazine.

Fever, which is a sign of inflammation, is a physiological process that occurs frequently in response to infection in patients in the ICU and is seen at rates up to 70% (16). In addition, fever is an important physical examination finding that shows whether the patient has recovered or not. Fever in septic patients has potential beneficial and harmful effects. Previous studies have shown that fever has positive effects such as antibody production, cytokine formation, increase of the neutrophil and macrophage functions, T-cell activation and induction of the heat shock response (33). Moreover, the rise in the temperature increases the antimicrobial activity by affecting the minimum inhibitory concentration of antibiotics (34). However, fever not only strengthens the immune response and inhibits bacterial and viral growth, but also increases the metabolic rate, rising oxygen consumption, which causes tissue hypoxia and deterioration in cardiac functions (16).

Most clinicians tend to apply pharmacological or mechanical antipyretic therapy in ICU patients developing fever. Antipyretics, which are routinely used in adult intensive care patients, especially

in those with volume depletion and predisposing factors, may cause renal or hepatic side effects and therefore, increase costs (33). In a recent meta-analysis of randomized controlled trials, Sakkat et al. examined whether temperature control is beneficial in febrile non-neuro critically ill patients with suspected or confirmed infection. It showed that although antipyretic treatment effectively lowered the temperature, it did not reduce hospital mortality, ICU length of stay, and shock reversal (16). In our study, fever treatment was individualized by the non-usage of antipyretics or mechanical cooling methods routinely, except in cases where fever is known to be harmful as body temperature rising above 40 °C, patients with limited cardiopulmonary reserve, acute cerebrovascular event, head trauma and possible pregnancy (33). Therefore, the potential benefits of fever, which are thought to have a positive effect on survival from infection, may have been exploited.

The current study has several strengths. First, the prospective and consecutive inclusion of patients in the study limits the possible selection bias. Second, to avoid potential confusion caused by the patient's agitation and pain, the participants were evaluated via the widely used and accepted scales. Third, a 'definite' drug-effect relationship, the highest ADR grading category, between chlorpromazine and hypothermia has not been described yet. Although the relationship was categorised as 'probable' according to the Naranjo assessment used in our study, the observed drug-effect relationship is highly suggestive of ADR (35,36). Our study has several limitations, also. First, the hypothermic outcomes have not been classified according to risk factors (24). Second, the laboratory workup and diagnostic approaches (for example, non-specific markers, clinical/radiological findings, and culture analyses), which may discriminate possible concomitant infections, have differed between groups due to less clinical suspicion in Group 1. If the standardisation between groups could be achieved, the evaluation of thermal homeostasis in infected patients would be supported by more accurate findings. Third, since only patients treated with chlorpromazine were included in the study, the hypothermic effect of other ADs have not been studied or compared. Fourth, patients with schizophrenia were excluded from the study, in agreement with the previous reports (8,26). This may introduce selection bias, although schizophrenia was present in only 2 of the otherwise eligible 116 patients. Future research should include such patients in order to ensure more accurate results.

Conclusion

In brief, using a single dose of chlorpromazine has shown an early onset of hypothermic effect. Severity scores and increased levels of inflammatory biomarkers could be predictive of ADR in ICU patients. Therefore, especially those patients repeatedly treated with chlorpromazine for sedation or with predisposing factors should have their body temperatures monitored continuously due to the possibility of thermoregulatory insufficiency, which may lead to hypothermia. Also, it should be noted that the severity of the disease and comorbidities developed during the treatment may increase the risk of hypothermia.

Financial disclosure

No financial disclosure was declared by the authors.

Conflict of interest

All of the authors declare that, there are no conflicts of interest in connection with this paper

References

1.Auerbach PS. Disorders due to physical and environmental agents. In: Ho MT, Saunders CE, editors. Current Emergency Diagnosis and Treatment, 3rd ed. East Norwalk, CT: Appleton & Lange; 1990. p. 422-425.

2.Delaney KA, Goldfrank LR. Hot and cold work environments. In: Rom WN, editor. Environmental and Occupational Medicine. Boston: Little, Brown; 1992. p. 1160.

3.Ruetzler K, Kurz A. Consequences of perioperative hypothermia. Handb Clin Neurol. 2018;157:687-697.

4.Niven DJ, Stelfox HT, Laupland KB. Hypothermia in Adult ICUs: Changing Incidence But Persistent Risk Factor for Mortality. J Intensive Care Med. 2016;31:529-536.

5.Boschi G, Launay N, Rips R. Neuroleptic-induced hypothermia in mice: lack of evidence for a central mechanism. J Pharmac. 1987;90:745–51.

6.Ginawi OT. Possible involvement of opioid receptors in moclobemide-induced hypothermia in mice. Pharmacol Res. 2003;48:237–40.

7.Asanami S, Shimono K. Species-level differences between mice and rats in regards to micronucleus induction with the hypothermia-inducing drug haloperidol. Mutat Res. 2009;676:102-5.

8.Van Marum RJ, Wegewijs MA, Loonen AJ, Beers E. Hypothermia following antipsychotic drug use. Eur J Clin Pharmacol. 2007;63:627-631.

9.Gocke E. Review of the genotoxic properties of chlorpromazine and related phenothiazines. Mutat Res. 1996;366:9-21.

10.Lopez-Munoz F, Alamo C, Cuenca E, et al. History of the discovery and clinical introduction of chlorpromazine. Ann Clin Psychiatry. 2005;17:113-135.

11.Adams F. Neuropsychiatric evaluation and treatment of delirium in the critically ill cancer patient. Cancer Bulletin. 1984;36:156-160.

12.Coppolo DP, May JJ. Self-extubations: A 12 month experience. Chest. 1990;98:165-169.

13.Robinson BR, Mueller EW, Henson K, et al. An analgesia-delirium-sedation protocol for critically ill trauma patients reduces ventilator days and hospital length of stay. J Trauma. 2008;65:517-26.

14.Adams F. Emergency intravenous sedation of the delirious medically ill patient. J Clin Psychiatry. 1988;49:22-26.

15.Marks W. Physical restraints in the practice of medicine: Current concepts. Arch Intern Med. 1992;152:2203-6.

16.Sakkat A, Alquraini M, Aljazeeri J, et al. Temperature control in critically ill patients with fever: A meta-analysis of randomized controlled trials. J Crit Care. 2021;61:89-95.

17.Dippel DW, van Breda EJ, van Gemert HM, et al. Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke: a double-blind, randomized phase II clinical trial. Stroke. 2001;32:1607-12.

18.Gramish JA, Kopp BJ, Patanwala AE. Effect of amantadine on agitation in critically ill patients with traumatic brain injury. Clin Neuropharmacol. 2017;40:212-216.

19.Gélinas C. Pain assessment in the critically ill adult: Recent evidence and new trends. Intensive Crit Care Nurs. 2016;34:1-11.

20.Severgnini P, Pelosi P, Contino E, et al. Accuracy of critical care pain observation tool and behavioral pain scale to assess pain in critically ill conscious and unconscious patients: prospective, observational study. J Intensive Care. 2016;4:68.

21.Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45.

22.Young DM. Risk factors for hypothermia in psychiatric patients. Ann Clin Psychiatry. 1996;8:93–97.

23.Turkish Society of Anaesthesiology and Reanimation Practice Guideline for Prevention of Unintentional Perioperative Hypothermia. Turk J Anaesth Reanim. 2013;41:188-90.

24.Kreuzer P, Landgrebe M, Wittmann M, et al. Hypothermia associated with antipsychotic drug use: a clinical case series and review of current literature. J Clin Pharmacol. 2012;52:1090-7.

25.Sessler DI. Perioperative heat balance. Anesthesiology. 2000;92:578-96.

26.Shiloh R, Weizman A, Epstein Y, et al. Abnormal thermoregulation in drug-free male schizophrenia patients. Eur Neuropsychopharmacol. 2001;11:285–288.

27.Sharma RP, Janicak PG, Bissette G, Nemeroff CB. CSF neurotensin concentrations and antipsychotic treatment in schizophrenia and schizoaffective disorder. Am J Psychiatry. 1997;154:1019–1021.

28.Zonnenberg C, Bueno-de-Mesquita JM, Ramlal D, Blom D. Hypothermia due to antipsychotic medication: A Systematic Review. Front Psychiatry. 2017;8:1-9.

29.Aslam AF, Aslam AK, Vasavada BC, Khan IA. Hypothermia: evaluation, electrocardiographic manifestations, and management. Am J Med. 2006;119:297–301.

30.Hale GM, Kane-Gill SL, Groetzinger L, Smithburger PL. An evaluation of adverse drug reactions associated with antipsychotic use for the treatment of delirium in the intensive care unit. J Pharm Pract. 2016;29:355-60.

31.Hellgren U, Julander I. Are white blood cell count, platelet count, erythrocyte sedimentation rate and C-reactive protein useful in the diagnosis of septicaemia and endocarditis? Scand J Infect Dis. 1986;18:487-8.

32.Reinhart K, Bauer M, Riedemann NC, Hartog CS. New approaches to sepsis: molecular diagnostics and biomarkers. Clin Microbiol Rev. 2012;25:609-34.

33.Kahveci F. Yoğun bakım hastalarında ateş-hipotermi. Turk J Intensive Care. 2008;6:7-12.

34.Mackowiak PA, Marling-Cason M, Cohen RL. Effects of temperature on antimicrobial susceptibility of bacteria. J Infect Dis. 1982;145:550-553.

35.Burk BG, Ward AH, Clark B. A case report of acute hypothermia during initial inpatient clozapine titration with review of current literature on clozapine-induced temperature dysregulations. BMC Psychiatry. 2020;20:290.

36.Goodbar NH, Foushee JA, Nash K, Connolly LA, Webster LM. Hypothermia associated with thioridazine use in an intellectually disabled patient. J Pharm Pract. 2016;29:250-2.