Influence of the type of anaesthesia used, the diet and the consumption of sugar and alcohol on the intradermal skin test to morphine

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Opioids are the drugs of choice for medium and high-intensity postoperative pain. Morphine is considered to be the most effective, but it can also lead to an increased risk of allergic reactions, including anaphylactic shock. A retrospective study was conducted, where postoperative positive intradermal skin tests to morphine of 90 patients with total abdominal hysterectomy and bilateral salpingo-oophorectomy were analysed. Patients were categorized in terms of the type of anaesthesia, diet, sugar diet and the amount of alcohol consumed. It was found that the type of anaesthesia significantly influences the frequency of positive intradermal skin test to morphine, which is most common in patients with general anaesthesia and endotracheal intubation (67% vs. 40%; \( P < 0.01 \)). There is a correlation between the type of anaesthesia and allergy to morphine, but not a very strong one. Diet and alcohol consumed had moderate influence on the frequency of positive intradermal skin test to morphine. There was no correlation observed between sugar consumption and allergy to morphine.

Keywords: morphine; intradermal skin test; anaesthesia; diet; sugar diet; alcohol consumption

Introduction

Treatment with subcutaneous or intravenous administration of morphine is often done without an intradermal skin test. It should be identified which factors are associated more frequently with positive intradermal skin tests to morphine, and, therefore, lead to an increased risk of anaphylactic shock when using morphine on these patients.

Abdominal hysterectomy and bilateral salpingo-oophorectomy can be followed by moderate to high-intensity postoperative pain. Prior to an abdominal hysterectomy, the patient undergoes a regional or general anaesthesia. In the absence of contraindications, neuraxial anaesthesia provides a better quality of recovery than general anaesthesia.\[1\] Minimizing the intensity of such pain maintains normal biological parameters, physical functioning and mental well-being. Opioids are the most effective analgesics used in these cases.

The American Society of Anesthesiologists agrees that anaesthesiologists who manage perioperative pain should use therapeutic options such as epidural or intrathecal opioids, systemic opioid – patient-controlled analgesia and regional techniques after thoughtfully considering the risks and benefits for the individual patient. They also agree that these modalities should be used in preference to intramuscular opioids ordered ‘as needed.’\[2\]

Morphine remains the most widely used opioid for the management of pain and is considered the gold standard to which other opioids are compared.\[3\] On the other hand, morphine induces histamine release which may cause an anaphylactic reaction or anaphylactic shock.\[4\]

Opioids can be useful for patients with acute pain such as that occurring after surgery, burn or trauma. The goal of such treatment is to provide adequate and timely pain management. Side effects caused by the use of opioids could be difficult to treat and the risk of their occurrence must be balanced against the benefits of pain relief.\[5\]

Opioids can equally affect endocrine, immunological and haematological functions and can even lead to severe allergic reactions. Allergenic determinants identified on morphine encompass the N-methyl group and the cyclohexenyl ring with a hydroxyl at C6. Cross-reactivity between morphine, codeine and other narcotics has been alleged.\[6\]

Intradermal skin test to morphine has a good sensitivity, but not specificity, because it induces histamine release. A false positive intradermal skin test can occur if high concentrations of morphine are used for testing (1/10,000 is the recommended dilution).\[7\]

There are a number of factors that influence the body’s response to the morphine action. Studies suggest that the
diet may have additional metabolic consequences. Among these are neurochemical changes in brain sites, some of which are also affected by drugs.[8]

It is known that diet and the consumption of sucrose and fatty acids in particular influence the response of rats to morphine.[9] The present study aims to examine whether there is a correlation between the diet of the patients and their intradermal skin test to morphine, as, to the best of our knowledge, there are no similar studies on that topic to date.

**Subjects and methods**

**Subjects**

This study reviews a large number of patients who underwent total hysterectomy with bilateral salpingo-oophorectomy receiving different types of anaesthesia, at a single centre. Patients who received part of their care at hospitals other than our centre were not included in an attempt to standardize factors that could potentially affect the outcome.

Exclusion criteria were:

- received oral or systemic corticosteroid within one month before this study;
- receiving immunosuppressive agents;
- taken antihistamine within three days before this study;
- previous history of immunotherapy;
- malnutrition;
- uncontrolled asthma;
- severe skin diseases;
- severe medical illnesses.

The final analysis included 90 patients.

**Study design**

The study design meets the criteria of medical and deontological ethics and the law of Romania and was approved by the Ethics Committee of the Faculty of Medicine and Pharmacy, ‘Lower Danube’ University of Galati.

**Anaesthesia**

The patients received spinal anaesthesia using bupivacaine 0.5% or general anaesthesia with endotracheal intubation, in which induction was performed with fentanyl (3 μg/kg), propofol (2 mg/kg) and succinylcholine (1 mg/kg). General anaesthesia was maintained with atracurium (0.1 mg/kg) and fentanyl (2 μg/kg) and recovery with atropine, neostigmine and pentazocine. Doses of the drugs used were chosen in accordance with the specifications of ‘Miller’s Anesthesia’.[10]

**Intradermal skin test to morphine**

Postoperatively, the patients were tested with morphine in the first 30 mins after surgery. In order to determine the risk of allergic reaction to morphine, an intradermal skin test was performed using 1 mL ampoules of morphine (20 mg morphine/mL) (Zentiva, Bucharest, Romania).

For the test, the explanations of the World Allergy Organization were taken into consideration and a concentration of 1/10,000 of morphine (1 mg/mL) was used. An 0.02 mL of dilution was injected into the dermis, using a hypodermic needle (29 Gx1/2’’) to raise a weal of 1–2 mm. Interpretation of the results was performed 20 mins after injection and was considered positive if the diameter area of erythema was at least two times larger than the diameter of the papule formed by the intradermal injection.

**Diet and alcohol consumption**

For the analysis, diet and alcohol consumption were statistically processed and analysed using data gathered from questionnaires completed by the 90 study participants. Alcohol consumption was between 11 mL and 33 mL of alcohol per day, sugar consumption was between 20 and 80 g of sugar per day and consumption of fruit and vegetables was between 300 and 700 g per day, for each study participant.

**Statistical analysis**

Data are summarized using the mean and standard deviation for normally distributed variables and the median and interquartile range for no normally distributed continuous variables. Patients were grouped based on developed a positive intradermal skin test to morphine or not, and univariate comparisons were made between the two groups, using $\chi^2$ test for categorical data and Fisher exact test for binary proportions. Two-tailed values of $P < 0.05$ were considered statistically significant. Data analysis was performed using the statistical package for social sciences (SPSS) software package (version 20.0, SPSS Inc., Chicago, IL).

**Results and discussion**

**Effect of type of anaesthesia**

The characteristics of the 90 patients included in the study were grouped according to the received type of anaesthesia, which can be seen in Table 1. A total of 58 (64%) patients underwent spinal anaesthesia and the other 32 ones (36%) received general anaesthesia with orotracheal intubation.

Of those 90 patients, 38 (42.2%) had a positive intradermal skin test to morphine. Of them, 19 (50%) received...
spinal anaesthesia and 19 (50%) received general anaesthesia. Among the patients who had a positive intradermal skin test to morphine, 39 (75%) received spinal anaesthesia and 13 (25%), general anaesthesia.

Of those 58 patients who received spinal anaesthesia, 39 (67.2%) had a negative intradermal skin test to morphine, and 19 (38.8%) had a positive intradermal skin test to morphine. Among the patients who underwent general anaesthesia, 13 (40.6%) had a positive intradermal skin test to morphine, and 19 (59.4%) did not.

It should be noted that general anaesthesia was associated with a positive intradermal skin test to morphine in a higher proportion of the patients than spinal anaesthesia.

Since the calculated value of Pearson Chi-square test ($\chi^2$) was 5.989 and the probability associated with this value is $P > 0.05$, it can be considered that there is a connection between the reaction to morphine and the type of anaesthesia. Since $P = 0.014 < \alpha = 0.05$, it can be said that the two variables (type of anaesthesia and positive intradermal skin test to morphine) are correlated, but the correlation is not a strong one.

Thus, the observed higher frequency of positive intradermal skin test to morphine after general anaesthesia than after spinal anaesthesia might be due to opioid derivatives being used in all three stages of general anaesthesia (fentanyl, in induction and maintenance; pentazocine in recovery), leading to opioids sensitization. However, studies on fentanyl have revealed little or no release of histamine from mast cells and no release with associated cardiovascular effects.[11] The consensus is that fentanyl, sufentanil, alfentanil and remifentanil do not cause histamine release when normal doses of drugs are given intravenously.[12] Certain agents, including opioids, dextans, protamine and vancomycin, are thought to cause direct, nonimmunologic release of mediators from mast cells.

Mechanisms underlying these reactions are poorly understood but may involve specific receptors (e.g. opioids). [13]

Succinylcholine induces histamine release, but it is rapidly metabolized (elimination half-life of 0.65 min). Since the minimum surgical duration in our study was 45 mins, postoperative intradermal test to morphine was not influenced by the release of histamine secondary to succinylcholine administration.[14]

Atracurium causes histamine release only if it is injected too fast or used in a higher dose than 0.4 mg/kg. In order to avoid the release of histamine, the dose of atracurium used was 0.3 mg/kg, injected slowly.[15]

**Effect of diet**

We also aimed to determine whether there is any connection between the patient’s diet, sugar and positivity intradermal test to morphine. In the patient observation sheet, the amount of different types of food which the patients consume daily/weekly was not mentioned and rarely the average amount of chronically ingested alcohol was specified. We started from the idea that food with more additives can cause allergic reactions which could then be followed by a positive intradermal skin test to morphine. However, food allergy should be distinguished from non-immune reactions to food (e.g. lactose intolerance, irritable bowel syndrome, infectious gastroenteritis) and reactions to additives (e.g. monosodium glutamate, metabisulfite, tartrazine) or food contaminants (e.g. latex dust in food handled by workers wearing latex gloves), which cause most food reactions.[15] Almost any food or food additive can cause an allergic reaction, but the most common triggers include milk, soy, eggs, peanuts, wheat, nuts and seafood.[16]
Six international studies have found that between 1 and 10.8% of allergies occurred after consumption of seafood, peanuts, eggs and milk.[17] Allergic reactions due to fruits and nuts are between 0.1 and 4.3% and to vegetables, only 0.1 to 1.4%.[18]

There are no studies showing a direct link between allergies to different foods and intradermal test positive for morphine, but clinical manifestations of cutaneous allergic reactions (redness), depends on the vascular reactivity.[19] At the same time it has been demonstrated that the intradermal test is influenced by vascular reactivity and density of receptors on mast cell surfaces.[20]

Sugar consumption

We tried to determine if there is a link between patient diet and morphine positive intradermal test based on the speculation that obese patients might be presumed to consume a greater quantity of products, thus a higher risk of consumed additives is presented.

The results of this study concerning the consumption of sugar and positive intradermal skin test to morphine are summarized in Table 2. There were 38 patients who developed a positive intradermal skin test to morphine. Of the total, 24 (63.2%) had consumed sugar once a day, 7 (18.4%) —two to three times a day and another 7 (18.4%) had consumed synthetic sweeteners. Among the patients who had a negative intradermal skin test to morphine, 30 (57.7%) had consumed sugar once daily, 16 (30.8%) —two to three times a day and 6 (11.5%) had consumed synthetic sweeteners.

It was found that of the 54 (60%) patients who consumed sugar once daily, 24 (44.4%) had a positive intradermal skin test to morphine and 30 (56.6%) did not. Of the total, 23 (25.6%) had consumed sugar —two to three times a day, of which 7 (30.4%) had a positive intradermal skin test to morphine and 16 (69.6%) did not. Synthetic sweeteners were used by 13 (14.4%) patients and 7 (53.8%) had a positive intradermal skin test to morphine and 6 (42.6%) did not.

Since the calculated value of Pearson Chi-square test ($\chi^2$) was 21.39, its associated probability is $P = 0.343 > \alpha = 0.05$, there can be considered to be an association (connection) between the response to morphine and sugar consumption. As for the nominal level correlation coefficients, $\varphi = V = 0.154$, $C = 0.152$, $P = 0.343 > \alpha = 0.05$, we could say that the two variables (consumption of sugar and positive intradermal skin test to morphine) are not correlated.

Fruit and vegetable consumption

The correlation between the consumption of fruits and vegetables and positive intradermal skin test to morphine was also analysed. The results are shown in Table 3. Of the 38 patients with positive intradermal skin test to morphine, 1 (7.7%) had consumed fruits and vegetables daily, 8 (24.2%) —two to three times a week and 29 (65.9%) only once a week. It was observed that positive intradermal skin test to morphine manifested especially among patients who had not eaten fruits and vegetables.

Of the 52 patients who had negative intradermal skin test to morphine, 12 (22.64%) had consumed fruits and vegetables daily, 25 patients —two to three times a week and 15 only once a week.

Of the 13 patients who had consumed fruits and vegetables daily, only one (7.69%) had positive intradermal

| Table 2. Positive intradermal skin test to morphine depending on sugar consumption. |
|-----------------|-----------------|-----------------|
| Morphine allergy | Count | No | Yes | Total |
| Diet sugar/no sugar | | | | |
| Once a day | Count | 30 | 24 | 54 |
| % within diet sugar/no sugar | 55.6% | 44.4% | 100.0% |
| % within positive intradermal skin test to morphine | 57.7% | 63.2% | 60.0% |
| % of total | 33.3% | 26.7% | 60.0% |
| 2–3 times a day | Count | 16 | 7 | 23 |
| % within diet sugar/no sugar | 69.6% | 30.4% | 100.0% |
| % within positive intradermal skin test to morphine | 30.8% | 18.4% | 25.6% |
| % of total | 17.8% | 7.8% | 25.6% |
| Synthetic sweeteners | Count | 6 | 7 | 13 |
| % within diet sugar/no sugar | 46.2% | 53.8% | 100.0% |
| % within positive intradermal skin test to morphine | 11.5% | 18.4% | 14.4% |
| % of total | 6.7% | 7.8% | 14.4% |
| Total | Count | 52 | 38 | 90 |
| % within diet sugar/no sugar | 57.8% | 42.2% | 100.0% |
| % within positive intradermal skin test to morphine | 100.0% | 100.0% | 100.0% |
| % of total | 57.8% | 42.2% | 100.0% |
skin test to morphine, and of the 33 patients who had consumed fruits and vegetables —two to three times per week, 8 (24%) had a positive intradermal skin test to morphine.

The calculated value of Pearson Chi-square test ($\chi^2$) was 20.846 and this value has an associated probability of $P < 0.0001 < \alpha = 0.05$. This indicates that there was an association (connection) between the response to morphine and consumption of fruits and vegetables. As the values of correlation coefficients at nominal $\rho = V = 0.481 > C = 0.434$ and $P < 0.0001 < \alpha = 0.05$, it can be considered that the two variables (positive intradermal skin test to morphine and consumption of fruits and vegetables) are correlated, and the correlation is moderate.

### Alcohol consumption

The analysis of the possible interdependence between alcohol consumption and positive intradermal skin test to morphine can be seen in the data in Table 4. Of the 38 patients with positive intradermal skin test to morphine, 4 (10.53%) had consumed alcohol occasionally, 5 (11.16%) once a week, 22 (57.89%) —two to three times a week and 7 (18.42%) every day.

Of the 10 patients who had consumed alcohol daily, 7 (70%) had a positive intradermal skin test to morphine and among the 34 patients who had consumed alcohol —two to three times a week, 22 (64.7%) had a positive intradermal skin test to morphine. The positive intradermal skin test to morphine was even more common when patients had consumed more alcohol.

Since the calculated value of Pearson Chi-square test ($\chi^2$) is 20.317 and this value is associated with probability $P < 0.0001 < \alpha = 0.05$, it can be considered that there is a connection between positive intradermal skin test to morphine and the amount of alcohol consumed. Since the values of correlation coefficients at nominal $\rho = V = 0.475 > C = 0.429$ and $P = 0.000 < \alpha = 0.05$, it can be concluded that the two variables (positive intradermal skin test to morphine and the amount of alcohol consumed) were correlated, and the correlation is moderate.

### Final remarks

These findings could be explained starting from the mechanism of allergic reactions to food. The majority of food allergic reactions are mainly caused by immunoglobulin E (IgE) mediated hypersensitivity reactions.[21] However, food allergic reactions are not limited to IgE mediated reactions only as non–IgE mediated allergic reactions, immunoglobulin G (IgG) mediated reactions, both IgE and IgG mediated reactions or immune complex mediated responses may also occur.[22] The basophilic activation test is a very common test for prediction of food allergy in susceptible patients.[23] Mast cells also possess high-affinity IgE receptors (FceRI) that participate in the allergic reactions.[22]

Synthetic opioids such as pethidine, but also natural opioids (morphine, codeine) can cause release of histamine without specific IgE antibodies, from direct mast cell degranulation.[24] Stimulation by morphine induces release of histamine from cutaneous mast cell but not

| Diet fruits and vegetables | Daily | Count | % within diet fruits and vegetables | % within positive intradermal skin test to morphine | % of total |
|---------------------------|-------|-------|-----------------------------------|-----------------------------------------------|----------|
|                           |       |       | 12                  | 92.3%                     | 23.1%    | 13.3%   |
|                           |       |       | 1                   | 7.7%                      | 2.6%     | 1.1%    |
|                           |       |       | Total               | 100.0%                    | 14.4%    |         |
| —Two to three times a week|       |       | 25                  | 75.8%                     | 48.1%    | 27.8%   |
|                           |       |       | 8                   | 24.2%                     | 21.1%    | 8.9%    |
|                           |       |       | Total               | 100.0%                    | 36.7%    |         |
| Once a week               |       |       | 15                  | 34.1%                     | 28.8%    | 16.7%   |
|                           |       |       | 29                  | 65.9%                     | 76.3%    | 32.2%   |
|                           |       |       | Total               | 100.0%                    | 48.9%    |         |
| Total                     |       |       | 52                  | 57.8%                     | 100.0%   | 57.8%   |
|                           |       |       | 38                  | 42.2%                     | 100.0%   | 42.2%   |
|                           |       |       | Total               | 100.0%                    | 100.0%   | 100.0%  |

Table 3. Consumption of fruits and vegetables and positive intradermal skin test to morphine.
from other tissues mast cells or basophiles,[23] IgE specific for morphine and codeine has been also identified.

Taken together, the results from the present study suggest that the link between certain quantities of sugar, vegetables or alcohol and positive intradermal skin test to morphine could lead to the introduction of these parameters at least in patients that are expected to use morphine treatment. Further studies with a larger cohort of patients would be needed to establish a clear link between diet and optimal drug therapy that can be applied to patients.

Conclusions

The analysis of the experimental data showed that patients with general anaesthesia had an allergic reaction to morphine in a higher proportion of cases than those with spinal anaesthesia. An association was observed between a positive intradermal skin test to morphine and sugar consumption, but there was a moderate correlation between this test and the consumption of fruits and vegetables. There was also an association between the response to intradermal skin test to morphine and alcohol, and the correlation between them was moderate. The statistical calculations of the link between certain quantities of sugar, vegetables or alcohol and positive intradermal skin test to morphine could lead to the introduction of these parameters at least in patients that are expected to use morphine treatment.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Table 4. Alcohol drinking and positive intradermal skin test to morphine.

| Drinking alcohol | Count | % within drinking alcohol | % within positive intradermal skin test to morphine | % of total |
|------------------|-------|--------------------------|----------------------------------------------------|-----------|
| Occasionally     | 22    | 84.6%                    | 42.3%                                              | 24.4%     |
|                  | 4     | 15.4%                    | 10.5%                                              | 4.4%      |
|                  | 26    | 100.0%                   | 28.9%                                              | 100.0%    |
| Once a week      | 15    | 75.0%                    | 28.8%                                              | 16.7%     |
|                  | 5     | 25.0%                    | 13.2%                                              | 5.6%      |
|                  | 20    | 100.0%                   | 22.2%                                              | 22.2%     |
| Two to three times a week | 12 | 35.3%                    | 23.1%                                              | 13.3%     |
|                  | 22    | 64.7%                    | 57.9%                                              | 24.4%     |
|                  | 34    | 100.0%                   | 37.8%                                              | 37.8%     |
| Daily            | 3     | 30.0%                    | 5.8%                                               | 3.3%      |
|                  | 7     | 70.0%                    | 18.4%                                              | 7.8%      |
|                  | 10    | 100.0%                   | 11.1%                                              | 11.1%     |
| Total            | 52    | 57.8%                    | 57.8%                                              | 57.8%     |
|                  | 38    | 42.2%                    | 42.2%                                              | 42.2%     |
|                  | 90    | 100.0%                   | 100.0%                                             | 100.0%    |
