



## Review paper

# The significance of race-related differences in anaesthesiological setting

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## ABSTRACT

**Introduction:** The human species shows a great variability. The differences involve culture, customs, appearance but they also come to include some biological or physiological aspects which have a potential bearing on the course of diseases and the effects of treatment. Over the recent years, the increasing globalisation and improved travel opportunities have resulted in a growing mass mobility. The arrival of people representing other ethnicities may pose a challenge to doctors traditionally offering treatment to individuals within ethnically homogenous societies.

**Aim:** The paper aims to present a comprehensive summary of state-of-the-art knowledge on race-related differences which may be of great importance for patient management in anaesthesiological setting.

**Material and methods:** This paper is based on the available literature.

**Results and discussion:** A literature review reveals a number of anatomical, pharmacokinetic and pharmacodynamic differences between the races. Moreover, particular ethnic groups show dissimilarities in the prevalence of some diseases requiring modifications in anaesthesiological management.

**Conclusions:** Prior to the commencement of treatment, patient's ethnicity and the consequent differences in terms of physiology should be recognised and considered in the treatment to ensure it is conducted appropriately and safely.

## 1. INTRODUCTION

The concept of race is a very difficult issue, not only because it is emotionally loaded, but also due to its enormous complexity. Our ethnic background is of great importance as it determines who we genetically are and in some populations there have been identified alleles accounting for 100% of alleles' variants (e.g., TPMT\*3C in the Nigerian population).<sup>1</sup> Over the years, scientists have failed to reach the consensus on how many races can be identified within the human species. The origins of the variation go back to *Homo sapiens* migrations, which saw their beginnings 50000 years ago.<sup>2</sup> It was then that the early man left Africa and started to settle in other territories from the Middle East, to Europe and Asia, finally reaching Oceania, which he colonised only 2000 years ago.<sup>2</sup> The expansion to other territories was thus a slow-paced process and people inhabiting similar regions of the world share some characteristics. The differences developed gradually, as a manifestation of human adaptation to another climate and different weather conditions. Darwin put it with striking accuracy by writing that drawing clear lines i.e. differentiating between the races is virtually impossible, as they merge swiftly into one another.<sup>3</sup>

However, for the purpose of this paper, we needed a clear race classification system. We decided to adopt the most classic one, comprising three main human races: white (Caucasian), black (Negroid) and yellow (Mongoloid) (Table).

## 2. AIM

One of the many effects of globalisation is migration of people on a huge scale. This leads to a growing ethnic diversity in societies which were traditionally largely homogenous. Doctors are increasingly faced with situations when they are to treat patients coming from different ethnic groups. Addressing these clinical needs, the paper is an attempt to present the state-of-the-art knowledge regarding the impact of race-related differences on the resulting need to modify anesthetic management of patients.

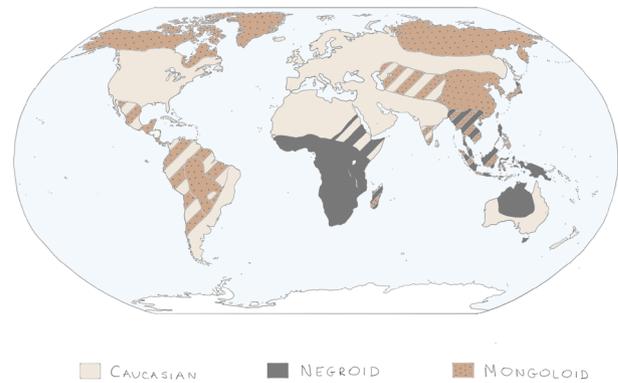
## 3. MATERIAL AND METHODS

This paper is based on the available literature. The primary sources are publications available in the PubMed and Google Scholar. We searched for articles using keywords: 'anesthesia,' 'anesthesiology,' 'intensive care,' 'ethnic differences,' 'racial differences,' and 'drug names.'

## 4. RESULTS AND DISCUSSION

### 4.1. Local anesthetics

Following intravenous administration of lidocaine, no significant differences are observed in pharmacokinetics (distribution volume, total plasma clearance, biological half-



**Figure. Simplified distribution of races around the world.**

life) or lidocaine binding to serum proteins between young white, black and yellow adults.<sup>4</sup> As already mentioned, a large amount of melanin makes the skin less penetrable for lidocaine and prilocaine, the ingredients of eutectic mixture of local anaesthetics (EMLA), which causes its delayed effect in black people (Table).<sup>5,6</sup>

Asian patients anaesthetised with liposomal bupivacaine demonstrated a lower assessed intensity of pain, despite no greater opioid consumption than patients of Caucasian race during the first 72 h following the surgery.<sup>7</sup> The difference in numerical rating scale (NRS) score was by 0.5 lower in Asian patients.<sup>7</sup> The length of hospital stay did not differ between the groups of patients.<sup>7</sup>

### 4.2. General anesthesia

Propofol is routinely used worldwide, which entails its use in patients of different races. As a result of altered pharmacodynamics in a patient and, what follows, their increased sensitivity to propofol, the patient can be, instead of being sedated, inadvertently put under general anesthesia, when the patient's self-protective reflexes and spontaneous breathing are lost.<sup>8</sup> In a study by Lamptang et al. sensitivity to propofol was compared in relation to the race. The obtained results demonstrated that Indian population shows the highest sensitivity to propofol, followed by the black, yellow, and white race, the latter being the least sensitive. When administering propofol without target-controlled infusion (TCI) the above mentioned differences must be considered, and when TCI is used, one should ascertain that the applied protocol accounts for race-related differences (the protocol by Marsh and Schnider does not account for these). After termination of propofol infusion the time necessary to return to bispectral index (BIS) value recorded before propofol administration was 11 minutes for white patients from Italy, 12.5 minutes for patients from China and Malesia, and 22.1 minutes for Indian patients.<sup>8</sup> The average time which elapsed till eye opening was 11.63 minutes for white patients, 13.23 minutes for patients from China, 16.9 minutes for black patients and 22.3 minutes for Indian patients.<sup>8</sup> Mean arterial blood pressure during the induction of anesthesia fell by 20% in white patients and by 10% in black patients.<sup>9</sup>

The mental and sedative effects of diazepam regarding their intensity and duration in yellow and white races were

**Table. Summative chart.**

	White	Black	Yellow
<b>Anesthetics i.v.</b>			
Diazepam	–	–	Greater accumulation in tissues
Dexmedetomidine	No data available	No data available	–
Propofol	The lowest sensitivity	The highest sensitivity	Intermediate sensitivity
<b>Inhalation anesthetics</b>			
Desflurane	No data available	No data available	No data available
Isoflurane	No data available	No data available	No data available
Sevoflurane	Limited clinical significance	Limited clinical significance	Limited clinical significance
Nitrous oxide	No data available	No data available	No data available
Halothane	No differences (a small sample size)	–	No differences (a small sample size)
<b>Muscle relaxants</b>			
Succinylcholine	Prolonged apnea may occur	A rise in potassium concentration may occur	–
Vecuronium	–	Worse intubation conditions with the dose of 0.1 mg.kg-1	–
Rocuronium	Optimal dose: 0.6 mg/kg A faster spontaneous resolution of n-m blockade	–	Optimal dose: 0.9 mg/kg A slower spontaneous resolution of n-m blockade
Cisatracurium	No differences	–	No differences
<b>Opioids</b>			
Fentanyl and remifentanyl	A shorter duration of anesthesia	A longer duration of anesthesia	Slower fentanyl metabolism
Morphine	No conclusive results	No conclusive results	No conclusive results
Pethidine	The fastest elimination rate	Intermediate elimination rate	The slowest elimination rate
<b>Local anesthesia</b>			
Lidocaine	No differences	No differences	No differences
Bupivacaine	A higher score on NRS	No data available	A lower score on NRS
<b>Other</b>			
Paracetamol	Increased metabolism of the drug carries a higher risk of toxic metabolite production, a shorter duration of action	Faster absorption with oral administration; decreased drug metabolism carries a lower risk of toxic metabolite production, a longer duration of action	Decreased drug metabolism carries a lower risk of toxic metabolite production, a longer duration of action

comparable, while repeated administration of the drug may result in increased accumulation of diazepam in blood and tissues in Asians.<sup>10</sup> For instance, when the same dose is taken every 24 h, after the 10th dose the patients of the yellow race will show about 40% higher levels of the drug in serum and about 48% higher drug levels in the tissues than Caucasians.<sup>10</sup> The yellow race is characterised by a slower CYP2C19 cytochrome metabolism than in black or white race, which makes the representatives of this race more susceptible to the toxic effect of diazepam and its metabolites.<sup>6</sup>

Dexmedetomidine considerably lowers blood pressure and catecholamine concentration in plasma.<sup>11</sup> There is a significant interindividual variability in the reduction of diastolic blood pressure (range of 1–34 mm Hg) and plasma noradrenaline concentration (range of 24–424 pg/mL).<sup>11</sup> There are no differences between black and white individuals in their response to dexmedetomidine.<sup>11</sup>

### 4.3. Inhalation anesthetics

In 2004 Edwin Liem et al. published the results of the study presenting evidence that women whose red hair colour is the result of a mutation in the gene for melanocortine-1 receptor had significantly higher requirement for desflurane than black-haired women.<sup>12</sup> One can therefore infer that also other genes, including those influencing race-related differences, will contribute to alterations in pharmacokinetics and pharmacodynamics of the remaining inhalation anesthetics.

Minimum alveolar concentration (MAC) for sevoflurane is by 24% higher in the Jewish populations from the region of the Caucasus Mountain range (Azerbaijans, Afghans, Iranians etc.) than in Europeans. The average MAC value was demonstrated for oriental patients (Lebanese, Moroccans, Syrians etc.).<sup>13</sup> The authors admit that, apart from the fact that immigrants from Caucasus tended to remember more details while under anesthesia in comparison to other patients included in the study, the above mentioned results are of minimal clinical importance.<sup>13</sup>

The preview of literature on inhalation anesthetics revealed there is paucity of research into the subject of ethnic differences and the use of desflurane, isoflurane or nitrous oxide. The available studies were often conducted on small samples and involved drugs which are no longer in common use such as halothane, with MAC showing no significant differences in the population of 42 patients from Asia and Europe.<sup>14</sup>

#### 4.4. Analgesics

Genetic variations between ethnic groups may suggest that the effects of some analgesics may differ. In a study by Faucett et al. the highest sensitivity to pain was observed in black, followed by yellow patients, whereas white patients showed the lowest sensitivity to pain.<sup>15</sup> The study also demonstrated that in every ethnic group men showed a higher tolerance for pain than women.<sup>15</sup>

Genetic factors, such as catechol-O-methyltransferase gene and opioid receptor gene (OPRM1) may also have an effect on sensitivity to pain.<sup>7</sup> Moreover, the differences in response to pain between ethnic groups may be associated with allele polymorphisms of pain-related genes.<sup>7</sup> For instance, the G-allele and OPRM1 polymorphism of 118 G are found more commonly in Asians (40%–50%) comparing to other ethnic groups, which may be associated with increased sensitivity to pain and varied response to its treatment.<sup>7</sup>

The studies show that Negroid patients need more time to recover from anesthesia with propofol and fentanyl or remifentanyl when compared to Caucasian race.<sup>9,16</sup> In Mongoloid race CYP3A4\*1G allele is relatively common, with the prevalence of 0.249% in Japan and 0.221% in China; in homozygotes it is responsible for decreased activity of CYP3A, and thus also slower metabolism of fentanyl.<sup>17</sup>

The reports on morphine present varying data. Some of them indicate there is a deeper respiratory depression expressed as a less pronounced reaction to the rise in  $P_{\text{CO}_2}$  and greater falls in arterial blood pressure in Caucasians when compared to patients from China.<sup>18</sup> Other reports demonstrate a more severe respiratory depression in Indian population than in other white individuals despite lower M6G serum concentrations in patients from India.<sup>19</sup> There are also studies denying any statistically significant differences between the Nepalese, the Chinese and Europeans in response to  $\text{CO}_2$  after the administration of morphine.<sup>20</sup>

Codeine is metabolised to its active form (morphine) by CYP2D6. The studies show that the representatives of the yellow race show little variability in codeine metabolism. Only 1% of the populations of China and Japan are ultrafast metabolisers, while fewer than 1% are poor metabolisers.<sup>6,21</sup> Decreased activity of CYP2D6, and the consequent weaker analgetic effect of codeine is manifested by as many as 6%–7% of Negroids and Caucasians.<sup>6</sup> On the other hand, even as many as over 15% of the Middle East population and North Africa are ultrafast metabolisers.<sup>21</sup>

Owing to the fact that Caucasians eliminates pethidine faster than the Nepalese and Chinese, caution is recommended with repeated administration of pethidine in patients of the yellow race as it carries a risk of drug accu-

mulation.<sup>22</sup> In conducted study pethidine consumption of Asians and Caucasians during 24 h postoperative period was 7.62 mg/kg and 9.97 mg/kg respectively.<sup>22</sup>

The urine reabsorption of conjugates of paracetamol metabolites with mercapturic acid and cysteine was found to be 9.3% in Caucasians, 5.2% and 4.4% in black people from West Africa (Ghana) and East Africa (Kenya), respectively.<sup>23</sup> There were no differences in paracetamol and sulphate conjugation.<sup>23</sup> It may indicate decreased metabolic activity of paracetamol in Africans, which may result in prolonged duration of action of this drug.<sup>23</sup> The yellow race shows faster absorption of paracetamol, with reduced production of glucuronide, but increased formation of sulphate conjugates and decreased production of cysteine and mercapturic acid conjugates compared to Caucasians, which may have a protective role against hepatotoxicity in the case of overdose.<sup>24</sup>

#### 4.5. Neuromuscular blocking agents

Ethnic differences in the effects of neuromuscular blocking agents (NMBAs) have been the subject of interest for many researchers. It all goes back to 1969, when Katz observed a distinct variability in the response to tubocurarine in Caucasians in New York and London.<sup>25</sup>

Fiset et al., inspired by Katz, proved that transatlantic differences are evident also for vecuronium, showing a more potent effect in Paris than in Montreal.<sup>26</sup> Another study investigated the effect of vecuronium in the dose of 0.1 mg/kg administered 60 s before intubation, which produced a much less satisfying effect in the Nepalese included in a study in Nepal than on patients of various ethnicities from Nepal participating in a study in Hongong. The suggested explanation pointed to differences in the distribution volume and muscle weight.<sup>27</sup>

The available literature focuses primarily on differences in the effects of rocuronium between the white race and yellow race. A study by Lee et al. demonstrated that to achieve better intubation conditions in a shorter time in Asian patients rocuronium should be administered in the dose of 0.9 mg/kg,<sup>28</sup> and not 0.6 mg/kg, as it is recommended in the Summary of Product Characteristics. Rocuronium was also the subject of another study which showed that sugammadex reverses neuromuscular blockade faster than neostigmine, both in Caucasians and the Chinese, the recovery being about 5.7 faster in Chinese patients.<sup>29</sup> The situation is different when the blockade resolves spontaneously; recognised as statistically significant, the process is slower in adult patients from China ( $43 \pm 13$  minutes) than in Caucasian patients ( $33 \pm 10$  minutes).<sup>30</sup> Dahaba et al. pointed not only to ethnic but also geographical differences, presenting evidence that the effect and duration of action of rocuronium differ between white patients from North America and those from Austria. A multitude of factors might be involved here and contribute to this effect, including pollution levels, lifestyle choices, diet and individual background in its wide sense.<sup>31</sup> Unfortunately, there is paucity of data in literature regarding the association between the effect of rocuronium and the black race.

No differences were found between the white race and the yellow race in the effect of cisatracurium in the dose-response and time-course-of-action relationships.<sup>32</sup>

The autosomal-recessive deficiency of plasma cholinesterase, the enzyme necessary for the degradation of succinylcholine and mivacurium occurs most commonly in the population of white Europeans, while being virtually non-existent in sub-Saharan populations and in the yellow race.<sup>6,33</sup> The deficiency may lead to prolonged apnea after the administration of the agents mentioned above.<sup>6,33</sup> In Negroid race, in turn, the administration of succinylcholine may cause a rise in blood potassium levels, with the highest values observed about 10 minutes after administration.<sup>34</sup>

## 6. CONCLUSIONS

Literature confirms the existence of race-related differences in anatomy, variability in the prevalence of some diseases, or differences in metabolism of commonly used anesthetic agents.

The standards of patient management should be adjusted depending on their ethnicity.

Societies which, until recently, were racially homogenous are now becoming increasingly heterogenous and there is a growing need to promote knowledge about race-related differences in anesthesiological setting. This will, hopefully, improve the quality of treatment for patients representing particular ethnic groups.

### Conflict of interest

None.

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None.

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