Anaesthesiology Intensive Therapy 2012; 44: 35-41



# Sufentanil in anaesthesiology and intensive therapy

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**Abstract**

Sufentanil, a potent α-1 agonistic opioid, was synthesized in mid-1970s. It was introduced into clinical practice ten years later, gaining some popularity over the last twenty years. A piperidine derivative, sufentanil has been reported to be 6-10 times more potent than fentanyl, depending on the route of administration; it has been registered for intravenous, epidural and subarachnoid administration. Its reported off-label use has included intra-articular and intranasal administration; moreover, it has been applied as an adjunct in peripheral blocks. In the review, contemporary uses of sufentanil, together with detailed pharmacokinetics and pharmacodynamics are presented. The author concludes that the limited side effects of sufentanil, together with its attractive pharmacokinetic profile, should promote its wider use in clinical practice.

**Key words:** analgesic, opioid, fentanyl; analgesic, opioid, sufentanil; pharmacology, sufentanil

Anestezjol Intens Ter 2012; 44: 35-41

By the end of the 50s of the previous century fentanyl, a derivative of phenylethylamine, was synthesised in Belgium; its introduction into clinical medicine in the early 60s was a breakthrough in anaesthetic management and in other fields of medicine seeking the agents for effective, safe and controlled analgesia.

Compared to widely used morphine (since 1806) or meperidine (since 1939), the above properties were gradually almost exclusively identified with fentanyl; even today, this agent is applied for analgesia in the majority of surgical procedures (70-80%) in some centres [1, 2, 3].

Paul Janssen and co-workers, the authors of this epoch-making discovery, noticed that the replacement of a hydrogen atom in the opioid piperidine ring at the 4$^{th}$ position and the use of other chemical substitutes might substantially alter the opioid properties preserving the analgesic effects of the entire group of the drugs obtained [3, 4]. In the next decade, active fentanyl derivatives were synthesised (between 10 and 20) characterized by various pharmacokinetic and pharmacodynamic properties and clinical usefulness. Much later thanks to Goldstein and co-workers (1971) and Kosterlitz and colleagues (1977) as well as the discovery of a receptor essence nature of opioid actions, it was demonstrated that the piperidine ring modification was associated with variable affinity (1973) to different types and subtypes of opioid receptors [3, 5, 6]. Nevertheless, due to its common use, low cost and a number of clinical papers concerning fentanyl published worldwide, the remaining agents synthesised by Janssen and co-workers were not immediately appreciated. It could be assumed that the increasing complexity of procedures, cardiac and neurological, in particular, necessitated the search for opioid agents suitable for cardiovascular stabilisation during long-hour procedures [1, 4, 7]. Consequently, in the early eighties, the specific features of sufentanil (SUF), the thienyl derivative of fentanyl, were reconsidered.

Sufentanil is an opioid, which stands out from the other drugs of this group because of its fast onset and strength of analgesic action; compared to fentanyl, the potency of intravenous syfentanil is 5-10 times higher [5, 6, 8] whereas in the extradural space, its equianalgesic value is found to be 3-5 times higher [5, 7, 9]. Such properties make sufentanil the drug of the highest analgesic potential among all clinical opioids applied. This potential

is mainly associated with its high solubility in fats and easy penetration through the blood-brain barrier.

Sufentanil is available in ampoules (5 μg $mL^{-1}$, 50 μg $mL^{-1}$) and has been approved for intravenous administration, to the subarachnoid and extradural space. Once the formal conditions are fulfilled, the drug is also used for peripheral blocks, intra-articular and transmucosal analgesia [2, 5, 6, 7]. The doses used vary, depending on the type of anaesthesia, anatomical space of its administration and clinical conditions of anaesthetised patients.

According to the classic textbook of anaesthesia, the special feature of SUF is the haemodynamic stability even with incremental or total high doses of the drug [5]. This property is used in SUF mono-anaesthesia when high induction dose of the drug is given in a single injection over 2-10 min. The stable hoemodynamic effect is achieved in the dose range of 5-20 μg $kg^{-1}$, at the total dose of 15-30 μg $kg^{-1}$ [5, 7]. If the patient is premedicated and undergoes combined anaesthesia with volatile agents and anaesthetic infusions, the effective analgesic doses of SUF can be almost tenfold lower. Thus, the initial supply of the drug is 0.5-1.5 μg $kg^{-1}$ and the total procedure dose 2-3 μg $kg^{-1}$ during medium-long surgery. The supplemental doses in both methods mentioned are comparable, i.e. 0.15-0.7 μg $kg^{-1}$ [5, 7, 8, 9, 10]. This enables to reach the concentration of about 1.25 ng $mL^{-1}$, which markedly reduces MAC of the inhalation anaesthetics used.

It appears that neonates and small children do not require reduced total or single doses of the drug (recommended doses: neonates – 5-15 μg $kg^{-1}$, children aged 3-12 years of age 5-20 μg $kg^{-1}$), and compared to adults, the margin of safety is provided by higher clearance of sufentanil [11, 12]. Despite its beneficial profile, sufentanil is not recommended for general anaesthesia for Caesarean sections; even though its concentration in the foetal blood is 20% lower than that in the maternal plasma, it may still induce opioid-related side effects in neonates [5, 7]. Such limitations do not regard central blocks [13, 14, 15] as with SUF administered to the extradural space, stable anaesthesia is obtained at low concentrations of drug in the systemic circulation. The recommended dose is 0.5-1 μg $mL^{-1}$ for low concentrations of local anaesthetics. At higher concentration of blocking agents their potency and speed of action is improved using the doses ranging from 0.25 to 0.75 μg $kg^{-1}$. Administered subarachnoidally, the drug shows its expected efficacy within the dose range of 2 μg-10 μg, most commonly – 5 μg (lower limb and urology surgery), which accelerates the action, prolongs the time of analgesia and increases the analgesic strength of block anaesthetics [7, 15, 16, 17, 18]. It should be clearly stressed that this also concerns central blocks for Caesarean sections or analgesia during natural deliveries when sufentanil has no negative adverse effects on the condition of a foetus and its recorded concentration in the umbilical blood is low [19, 20].

The transmucosal (intranasal) administration of SUF is controversial as its bioavailability ranges markedly from 46 to 71%. The administration is unpleasant (burning sensation) and can induce the thorax rigidity, particularly in children. However, there are some reports demonstrating high analgesic effectiveness for post-operative or chronic pain management and for premedication. The suggested intranasal doses of SUF are 2 μg $kg^{-1}$, nevertheless, the bolus dose of 0.025-0.05 μg seems to be more useful for all patients. In most cases, the drug is prepared by a hospital dispensary [21].

The listed doses of SUF provide effective, although highly varied analgesic plasma concentrations. The plasma SUF concentration abolishing the haemodynamic reaction to intubation is 1.08 ng $mL^{-1}$, ranging from 0.73 to 2,55 ng $mL^{-1}$. In non-premedicated patients, its concentration eliminating the response to a standard surgical stimulus is twofold higher (2.08±0.62 ng $mL^{-1}$) [5, 6, 7].

The doses of SUF in the continuous infusion range from 0.3 to 1 μg $kg^{-1}$ $h^{-1}$. The safety of this management is determined by its context-sensitive half-time, compared to fentanyl. The index mentioned is the time in which the concentration of SUF after discontinuation of its continuous infusion is halved. After the 4-hour supply, its value is 30-35 min, although with the increasing time of infusion it gradually increases (non-linearly). Following the 12-day infusion in analgosedation this time is slightly more than 4 hours. More importantly, the several-day infusion of SUF (>7 days) is likely to lead to addiction with possible withdrawal symptoms. In some countries, SUF for complex sedation was not approved, as accurate assessment of this parameter is infeasible [5, 7, 22].

Moreover, some more precise tools for control of plasma SUF were introduced, i.e. a target control infusion (TCI). In various clinical trials, it is assumed that during combined anaesthesia with volatile or intravenous anaesthetics, the drug should be maintained in the target compartment of 0.2-0.4±0.2 ng $mL^{-1}$.

The described fluctuations in plasma levels of SUF result from at least three-compartmental pharmacokinetics of the drug, possible variability of structure and number of opioid receptors under various clinical conditions. For these reasons, the doses of SUF have to be significantly increased; such infusion doses are well tolerated in acute inflammations during colectomy compared to conservative procedures – 1.24±0.48 μg $kg^{-1}$ $h^{-1}$ *vs* 0.62±0.3 μg $kg^{-1}$ $h^{-1}$, respectively; $p<0.05$ [25]. From the practical point of view, the SUF action during extracorporeal circulation procedures is also of importance, in which marked fluctuations are observed due to secondary redistribution from the lungs and muscles following a primary decrease in the drug concentration, mostly resulting from haemodilution and redistribution to the cardiopulmonary depot. This substantially prolongs the half time of elimination (>12 h) [5, 6, 26]. In practice, prolonged postoperative surveillance is required.

In each case, the analgesic action of SUF is agonistic, mainly with the m-1 receptor, and consists in binding the drug with the receptor amino acid chain, which punctures the effector cell membrane seven times (7TM). The specific "pocket" that the opioid penetrates, changes the receptor configuration and the drug binds to the α subunit (a specific G membrane protein). Under such

conditions, the α subunit-coupled GDP 'interchanges' with GTP and the α subunit binds with adenylyl (adenylate) cyclase, which leads to the formation of cyclic adenosine monophosphate (cAMP). During the reaction, the activity of adenylyl cyclase and cAMP alters. The remaining subunits stimulate the mitogen-activated protein kinase (MAPK), which is thus involved in the activation of the post-inflammatory chain of eicosanoids. This effect closes the calcium channels and removes potassium ions from the cell, which results in hyperpolarisation of the neuron and inhibited conduction of stimuli [2, 3, 8, 27, 28]. At this point, possible changes in the activity of opioid receptors (affected by various factors, e.g. inflammation) and their membrane density due to exposure to agonists, is worth stressing [7, 25]. The described mechanisms of analgesic action of opioids also regard μ, κ and δ receptors.

The mechanisms mentioned result in central and peripheral inhibition of nervous conduction and release of neurotransmitters and substance P in the posterior horns of the spinal cord. Moreover, hyperpolarisation affects the interneurons of the spinal cord and cerebral structures, in particular, the cerebral aquaduct, raphe nucleus and blue (as in cases of other opioids). These brain regions are rich in opioid receptors, hence can produce biogenic amines responsible for emotional reactions to the opioids used. The differences in the reaction of receptor activation by opening only one ion channel and maintaining the other one closed depends on the type of a receptor and its location. Furthermore, besides SUF spinal and supraspinal effects, presynaptic and postsynaptic inhibition can be observed as well as possible effects on the GABAergic interneuron complex of CNS. The action of SUF within the brain is variable; thus, some papers emphasise only moderate sedative and hypnotic effects of the drug yet complete analgesic efficacy [5, 6, 27, 29]. Moreover, weaker action of sufentanil within the μ-2 receptor as compared to κ 1-3 and δ 1-2 receptors have been demonstrated [30].

All the receptor effects of opioids via the G protein system and MAPK are associated with multidirectional metabolic influence of the drugs on the anaesthetised and/or sedated patient. This influence reaches far beyond the basic analgesic effect, which, among other things, is caused by close proximity of the autonomic nerve elements and opioid receptors. The effects on the endocrine system are worth stressing; the action of opioids leads to inhibition of the hypophyseal-adrenal axis and the release of gonadotropins and corticotropins, which results in decreased amounts of cortisol, testosterone, growth hormone and prolactin. Compared to morphine, such effects of fentanyl derivatives are profoundly stronger, which is stabilising under the surgical stress circumstances [28, 31, 32].

Intravenous SUF results in its transfer to the peripheral tissues (half-time of fast distribution 1.4 min); however an increase in its level at the site of administration is quite slow, 3-6 min to achieve its maximum effects, with relatively long periods of high concentrations after a single dose (half-time of slow distribution 17.7 min). The analgesic effect maintains for 30-50 min. Besides its lipophilic properties, the drug is characterised by high ionization and marked strength and range of coupling with plasma proteins (92.5-93%), including albumins and alpha-1-acidic glycoprotein, which consequently determined a low volume of distribution at balanced concentration, i.e. 123 L. For these reasons, it is important to achieve the dynamic balance between SUF concentration at the administration site and places of receptor binding of the drug while maintaining proportionality and parallelism of the process. This phenomenon is also used for dosage modifications during central blocks [5, 7].

After its single administration, the majority (96-98%) of SUF disappears from the plasma in about 30 min (time of minimal action) whereas its relative time of action ranges from 100 to 150 min. With doses of 250-1500 μg, the mean half-time elimination is 656- 938 min (784 min on average) and increases with the dose (at 1500 μg – about 16 h). It should be noted, however, that despite its prolonged time of elimination, SUF is simultaneously highly dynamically metabolised. It is metabolised in the liver and partially in the small intestine and the rate of metabolism is dependent on the effectiveness of hepatic flow and metabolic condition of the organ (e.g. hepatic porphyria is an absolute contraindication for SUF use). Therefore, the coefficient index rate of hepatic elimination of SUF reported in literature, i.e. 0.8, is a relative value. During porphyria, the drug is broken down mediated by N-dealkylation, oxidative O-demethylation and aromatic hydroxylation. The major metabolite, practically inactive, is N-phenyl-propanamide excreted over the period of 24 h; about 1-2% of SUF is also excreted in its unchanged form [3, 5, 6, 7,14, 30].

The rate of metabolism is also likely to be affected by the drugs of a similar metabolic pathway, particularly when their metabolism is mediated by cytochrome P450 3A4, which are often used for home or pre-hospital treatment (e.g. cymetidine, ranitidine). Ketoconazole, itraconazole and erythromycin, quite commonly applied, also belong to the drugs that can inhibit the metabolism of SUF. The action of other drugs is associated with interactions with the entire opioid group (benzobiazepines, blockers of β-receptor, inhibitors of MAO, etc.); and for this reason were not included in this paper.

At present, sufentanil is widely used during general anaesthesia for various surgical procedures, often in severely ill patients and when anaesthesia is expected to be long. The standard dosing includes the induction bolus of 1 μg $kg^{-1}$ and the maintenance dose of 1 μg $kg^{-1}$ $h^{-1}$, combined with midazolam in premedication and isoflurane (in typical doses) for anaesthesia maintenance, which in most cases eliminates the unanticipated effects [33]. The induction dose is often used before intubation. The literature data confirm high usefulness of SUF for circulatory stabilization, including children (0.2 μg $kg^{-1}$ 120 sec before intubation) [11, 12]. In short-lasting procedures, the single dose may be sufficient. Such doses (e.g. 0.1-0.3 μg $kg^{-1}$ or those described earlier) are occasionally used for prolonging analgesia and its continuation during the

postoperative period. Otherwise, in long-term procedures with significant autonomic stimulation, the continuous infusion of SUF is more frequently required in the form of TCI. In such cases, in abdominal surgeries, the sufficient target concentration of SUF in the central compartment should be 0.2 ng $mL^{-1}$ [24] or 0.25 ng $mL^{-1}$ at the total consumption of 0.28-0.41 μg $kg^{-1}$ $h^{-1}$ [9]. SUF administered using the TCI method provides optimal conditions for any surgical procedure; the extubation is not delayed and the risk of postoperative respiratory depression is avoided. This characteristic, combined with prolonged analgesia, makes the drug better than opioids of ultra-short halftime [9].

In each case of SUF use in combined anaesthesia, enhancement of its action in terms of sleep depth (benzodiazepines, propofol, ketamine, volatile anaesthetics) and neuromuscular blockade should be taken into account. The interaction can regard the effects of SUF on ion channels, particularly, the calcium one (action of agents of neuromuscular blockade or postoperative muscle rigidity) and on the ascending spinal cord (deepening of sleep, effects on the respiratory centre).

Since the dawn of its clinical use, sufentanil has become the preferred intravenous opioid under conditions of haemodynamic disturbances [4]. Its standard doses induce slight dilation of arteries, which results from its effect on the vasomotor centre and increased capacity of peripheral venous vessels [5, 33]. However, no direct negative impact on the dynamics of myocardial contraction is observed; simultaneously the consumption of oxygen is decreased and the basic rhythm slowed down. The beneficial haemodynamic reaction following SUF administration maintains even in cases of extremely potent autonomic system stimuli [8, 10, 12, 22]. Its beneficial effects are also noted in patients with existing ischaemic myocardial abnormalities [26].

Meticulous haemodynamic monitoring in this group of patients does not reveal significant changes in the cardiac index, ejection fraction or heart rate after the dose of 1-2 μg $kg^{-1}$. Moreover, the echocardiographically assessed systolic and diastolic function of the left ventricle is not found to be changed (E'/A' – 0.95 *vs* 0.89, p=0.110, E/E' 15.4 *vs* 14.9; p=0.612) [26]. Such specific properties of SUF have been also confirmed in *in vitro* isolated fibres of the myocardium: sufentanil and remifentanil have similar and well expressed protective effects on the myocardium [22].

Furthermore, SUF can be used in the mode of cardiosurgical 'fast track' and in paediatric patients with congenital heart defects, which corresponds with the previously presented data demonstrating limited effects of properly dosed sufentanil on the postoperative periods [34]. The inhibition of autonomic reaction is also useful in neurosurgical procedures, in which the stimulation from the operative field may be unpredictable. The other assets of SUF regard its use in awake patients and slight effects on the changes in the cerebral flow [35]. In standard intravenous doses, SUF reduces the risk of sudden arterial pressure changes and their consequences in neurosurgical patients [36]. Contrary to remifentanil, with its short context-sensitive half-time, the intraoperative use of SUF does not require morphine supplementation for postoperative analgesia due to prolonged analgesia and stabilisation of cerebral circulation. Considering possible, although not always present sufentanil-related prolongation of postoperative ventilation support, many centres prefer this agent due to its circulatory properties [8, 9, 23, 26].

From the practical point of view, the effects of sufentanil during epidural and subarachnoid anaesthesia are equally important. To put is simply, in such cases the extent of SUF action depends on its dose, volume and kind of anatomical space [5, 13, 19, 37, 38]. The local action and stimulation of preganglionic fibres of the autonomic system are mostly responsible for enforcement of analgesic effects of local anaesthetics and haemodynamic effects. Moreover, sufentanil acts agonistically towards the μ-1 receptor, most effectively stabilising the surgical stress reaction. For instance, the use of 0.3% ropivacaine and sufentanil during total prostatectomy suppresses successfully the stress response, documented e.g. by plasma levels of glucocorticoids, prolactin, adrenaline and noradrenaline [39]. Similar observations concerning endocrine reactions were noted in paediatric populations [40]. Moreover, the strength of such effects was confirmed using the continuous infusion of ropivacaine or levobupivacaine with SUF in the dose of 1 μg $mL^{-1}$ during thoracic surgeries [37]. The continuation of analgesic management after thoracotomy using the SUF infusion to the epidural space in the dose of 2.6 μg $h^{-1}$ with 10 mL of a local anaesthetic of various concentration showed high efficacy, despite opioid-associated adverse side effects (vomiting, nausea and pruritus) [41].

The similar analgesic management after knee arthroplasty using various local anaesthetics, at the same dose of SUF provided effective postoperative analgesia [48]. The optimal concentration of sufentanil for epidural anaesthesia with 0.3 % ropivacaine should be 0.75 μg $mL^{-1}$ [43].

In such cases, the standard indication for its use is to reduce labour pains of a parturient. The satisfactory and analgesia-stabilizing effect of SUF was observed during anaesthesia with ropivacaine and bupivacaine for spontaneous deliveries [38], although slower heart rate of a foetus is likely to occur when ropivacaine and sufentanil are combined [19]. Nevertheless, SUF in the doses of 0.25-0.45 μg $mL^{-1}$ at low doses of local anaesthetics is widely applied. Moreover, the degree of analgesia obtained during anaesthesia for deliveries using epidural SUF was found to be better than after intravenous remifentanil [44]. This may also be related to lower requirements for opioids in the parturient group, which was demonstrated in the study of almost 15 000 patients [45]. Similar indications were determined for SUF use during epidural anaesthesia for Caesarean sections, although the doses of local anaesthetics and opioids were generally higher.

Furthermore, sufentanil proved effective for subarachnoid blocks, in which the crucial factors for its

recommendation include: accelerated analgesic effects, higher analgesic potency of anaesthesia and longer blockade. Those data are fully confirmed by literature findings. The standard SUF doses enhancing analgesia and stabilising haemodynamics of an adult range from 1.25 to 7.5 μg, in most cases – 5 μg, which combined with a local anaesthetic enables its use in various, other than obstetric, procedures [46].

The randomized prospective study on the efficacy of SUF in lower limb surgeries demonstrated a fast onset of action and prolonged analgesia after subarachnoid anaesthesia. Unfortunately, in most patients its use results in short-term pruritus [47], which can be substantially limited using lower doses of SUF, i.e. 1.5 μg [48]. Under subarachnoid anaesthesia, haemodynamic stabilisation of parturients and lack of negative opioid effects on newborns are worth emphasizing [49], which also regards patients undergoing prostatectomy [50]. The subarachnoid administration of 5 μg of SUF decreases $ED_{50}$ of hyperbaric ropivacaine providing a significantly lower range of motor blockade [51].

Another effect of subarachnoid SUF is stabilisation of hormonal response comparable to the earlier described intravenous and epidural supply. The reaction at high doses of the drug was found even better expressed during subarachnoid than intravenous administration [31].

The cited results of clinical trials provide convincing grounds for the use of SUF in regional anaesthesia for obstetric and other procedures and in each case where circulatory stabilisation is necessary.

Sufentanil has also been found useful for treatment of ITU patients as a part of sedative management. Considering the properties of sufentanil described earlier, the search for an analgesic stabilising haemodynamics of patients naturally focused on this agent. Numerous inconveniences associated with the use of morphine and fentanyl as well as the painful procedure additionally contributed to the further quest for other solutions concerning analgesic sedation in intensive therapy [52, 53].

In adults, the use of morphine and fentanyl is gradually reduced in favour of sufentanil and remifentanil. The transitory abandonment or weakening of sedation is easier in cases of remifentanil than sufentanil; however, the benefits are inconclusive and in some cases (CNS injuries), the management in question is even contraindicated. Therefore, SUF appears to be a good alternative to other opioids used for analgosedation, providing stable circulatory conditions and satisfactory analgesia. Our observations indicate that effective analgesic doses of SUF can be reduced using the so called CNS protective sites of drug uptake, by combining the opioid with several other drugs (multimodal sedation), directed at specific structures and mediators of the nervous system [53, 54]; hence general action of SUF and specific inhibition of cortex damaging mediators is utilised.

Sufentanil induces side effects characteristic of all opioids, although due to its specific molecular structure, some of them are differently manifested. Compared to fentanyl, it shows markedly lower tendency to induce nausea and vomiting. Moreover, euphoric symptoms are also less common and less severe due to limited effects on dopaminergic structures of the nucleus reccumber and lateral tegmental field. Likewise, its influence on the cerebral flow is less manifested, compared to fentanyl. The commonly addressed complication associated with single doses of SUF is bradycardia; however, it should be stressed that it is usually caused by too fast administration of the drug. In some centres, the induction dose of sufentanil is preceded by atropine. The fast administration of the drug also induces early (after several tens of seconds) and late (after several hours) rigidity of thoracic muscles. Its nature remains unknown. The majority of data speaks in favour of the central mechanism, as the symptom can be abolished with naloxane; nevertheless, the selective impact on calcium channels cannot be excluded. Another commonly described SUF-related complication, especially in central blocks, rarely in general administration, is pruritus. Despite the SUF-induced release of histamine from basophils, the nature of post-opioid pruritus does not seem to be directly related to this phenomenon; naloxane causes its gradual subsidence yet at much slower rate than in other SUF side effects [3, 5, 6, 7].

The multi-directional analysis of benefits of SUF in clinical medicine should also consider economic aspects. The comparison of three major opioids used for the surgical "fast track" revealed the lowest cost-effectiveness of remifentanil, medium of sufentanil and the highest of fentanyl (140.54 *vs* 43.33 USD, $p<0.01$) [61]. However, the total cost of treatment of patients anaesthetised with various opioids did not significantly differ: 7841 USD for fentanyl, 5943 USD for sufentanil and 6286 USD for remifentanil, $p>0.05$). The time of mechanical ventilation in all groups of patients was comparable (167, 285 and 234 min, respectively; $p>0.05$), which is also true for the duration of post-operative room stay ( 18.8, 19.8, and 21.5 h, respectively; $p>0.05$) and total cost of treatment (5 days). The literature data demonstrate that the apparent economic effects achieved with fentanyl are quickly eliminated by the required supplementary treatment and therapy of complications [55]. Considering the pharmacoeconomics and the available clinical data, the choice should regard sufentanil versus remifentanil, according to the clinical demands. Such an approach appears to be worthy of popularisation among Polish anaesthetists and intensive care therapists.

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received: 01.09.2011 r.
accepted: 27.12.2011 r.

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