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Brief Report

Aqueous leaf extract of *Olea hochstetteri* modulates thiopentone- and ketamine-induced anesthesia in rats

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Key Words
Anesthetic modulation; *Olea hochstetteri*; Phytotherapy

Abstract

Objective: Traditionally, olive (*Olea hochstetteri*) leaves are used as hypotensive, antinociceptive, hypnotic, hypoglycemic and antipyretic agents. However, its influence on anesthetic effect of thiopentone and ketamine has not yet been clarified.

Methods: All experiments were carried out on adult Wistar rats. Graded concentrations (100, 200, 400 and 800 mg/kg) of the aqueous leaf extracts of *Olea hochstetteri* were administered to one group of rats immediately following thiopentone sodium administration and another group immediately following ketamine hydrochloride administration intraperitoneally. The time for the anesthetic effect was recorded using the righting reflex.

Results: There was significant increase in the sleeping time of rats in both thiopentone- and ketamine-induced anesthesia following the administration of the *Olea hochstetteri* leaf extract.

Conclusion: The present results suggest that aqueous leaf extract of *Olea hochstetteri* extends thiopentone- and ketamine-induced anesthesia. This is of particular importance to the anesthesiologists so that peri- and post-operative safety measures are implemented with the routine use of phytotherapy.

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INTRODUCTION

The first recorded medicinal herbarium was incremented by the Chinese Emperor Shen Nung (2838-2698 BC), who catalogued approximately 365 medicinal herbs and poisons [1]. The universal role of plants in the treatment of diseases is exemplified by their employment in all major systems of medicine irrespective of the underlying philosophical premise. Historically, herbs have been used to produce anesthesia. Dioscorides (40-90 AD), the Greek military physician, described the drinking of the mandrake by patients to cause insensibility during surgery [2]. Medicinal herbs and/or vegetable origin principles may participate in the basic triad of anesthesia: analgesia, amnesia, and microrelaxation, added to autonomic stability maintenance [3].

The olive tree (*Olea hochstetteri* B; Oleaceae) has been cultivated in the Mediterranean for more than a thousand years. *O.hochstetteri* leaves have been used for medicinal purposes, and were introduced recently into the European Pharmacopoeia (Ph.Eur.). The acqueous leave extract of the plant has been used to cure rheumatic and neuralgic diseases [4], febrile illnesses, hypertension, arteriosclerosis and diabetes [5]. The olive leaf has been shown to contain the active iridoid constituent oleuropein, secoiridoids such as ligustroside, oleuroside, and un-conjugated secoiridoid aldehyde [6]. Triterpenes and flavonoids, including luteolin, apigenin, rutin and diosmetin, are also present. Oleasterol, leine, and glycoside oleoside have also been found in the leaves [7]. *O.hochstetteri* leaf has been shown to contain reducing sugars, saponins, garlic tannins, alkaloids [8] and other constituents like sterols and triterpenes.

Calcium ion channel-blocking activity from the olive leaf extract has been documented [9]. Ca^{2+} has a physiological role in the regulation of pain sensitivity, and inhibition of calcium movement contributes to

antinociception [10]. Several other plants have been shown to modulate the anesthetic effects of some drugs including herbal monoterpene alcohols [1, 11]. *O.hochstetteri* has been used by the traditional healers of Morogoro region of Tanzania in the treatment of non-insulin dependent diabetes mellitus [12]. The plant has also been found to have antibacterial action against *Staphylococcus aureus*, *Salmonella typhi*, and *Pseudomonas aeroginosa* [13].

The routine use of phytotherapy, diet complementation with products of vegetal origin or a vegetarian diet should be part of the pre-anesthetic or anesthetic evaluation questionnaire, so that preventive measures are taken against possible drug interaction and peri/post-operative safety measures implemented [2, 14, 15]. Although *O.hochstetteri* is widely used among the many peoples of the African continent, its modulatory activity on some commonly used anesthetic drugs is lacking. This study therefore, aims to determine the influence of aqueous leaf extract of *O.hochstetteri* on sleeping time induced by thiopentone sodium and ketamine hydrochloride.

MATERIALS AND METHODS

Plant materials

The leaves of the olive tree (*O.hochstetteri*) were obtained from a rural community in Borno state, Nigeria. It was identified and authenticated as *O.hochstetteri* by a botanist of the Department of Biological Sciences, University of Maiduguri, Nigeria, and a voucher specimen number Vet 206A was deposited in the Department of Veterinary Physiology and Pharmacology, University of Maiduguri. After collection of the leaves, the samples were air-dried in the shade for 14 days. They were ground into fine powder and sieved to remove any coarse plant materials. Two hundred and fifty grams (250 g) of the powder was exhaustively extracted with distilled water using the reflux method [16]. The crude aqueous extract was then concentrated *in vacuo* and yielded the extract (6.1%, w/w). The extract was stored as a stock solution at 4°C until used.

Preliminary phytochemical screening, toxicity study and anesthetics

The active components of the *O.hochstetteri* leaf were determined at the Departments of Pharmacological Chemistry and Pharmacognosy, University of Maiduguri, Nigeria according to standard methods [17] and the LD_{50} calculated as 1250 mg/kg body weight (BW) as earlier reported [8]. Thiopentone sodium and ketamine hydrochloride were obtained from Rotex Medica (Tritau, Germany).

Experimental animals

A total of 60 outbred adult Wistar rats of both sexes weighing between 124 and 184 g were used for the study. They were maintained in rat cages in the Physiology laboratory of the Faculty of Veterinary Medicine, University of Maiduguri, Nigeria. Pelleted commercial feed (ECWA, Nigeria Plc., Jos, Nigeria) and water were provided *ad libitum*. The rats were allowed 21 days to acclimatize to their new environment before the commencement of the experimental study. The Animal Welfare Committee of the Faculty of Veterinary Medicine, University of Maiduguri, Nigeria approved this experiment (No. FVM699/02/6735) and the experimental animals were handled in accordance with the internationally acceptable principles for laboratory animal use and care [18].

Experimental design

The rats of both sexes were randomly separated into twelve groups (A-L) of 5 rats each in clean plastic rat cages. In the first experiment, four groups of rats (B-E) were each injected with thiopentone sodium intraperitoneally (IP) at a dose of 30 mg/kg BW immediately followed by increasing doses of the *O.hochstetteri* leaf extract (100, 200, 400, 800 mg/kg BW, respectively). Groups A and F were injected with thiopentone sodium and normal saline, respectively, which served as positive and negative control groups.

In the second experiment, rats in groups H-K were injected with ketamine hydrochloride IP at a dose of 30 mg/kg BW immediately followed by increasing doses of the leaf extract as outlined in the first experiment while groups G and L were injected with the ketamine hydrochloride and saline, respectively.

The anesthetic effects were evaluated following the drugs and extract administration. Time of anesthetic effect was measured when the rats did not right themselves within 30 seconds after being placed in a supine position, namely the righting reflex, in accordance with the method of Fassoulaki *et al* [19].

Statistical analysis

Data obtained were expressed as mean ± standard deviation and statistical significance between control and treated groups in the present study was determined by one-way analysis of variance using GraphPad software (San Diego, CA, USA).

RESULTS

The state of anesthesia was assessed by observing the loss of righting reflex within the first few minutes after the administration of the anesthetic drugs and the extract. The thiopentone sodium-induced anesthetic

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effect in the positive control group (A) lasted 12 ± 2.74 min. In groups B-E, administration of thiopentone sodium followed by the graded doses of *O.hochstetteri* leaf extract of 100, 200, 400 and 800 mg/kg BW, respectively, enhanced the anesthetic effect in all the groups but significantly more in groups C, D and E (Fig.1; $P < 0.001$) while rats in the negative control group (F) did not show any sedative effect (0 ± 0.0)

Similarly, in the second experiment, ketamine hydrochloride-induced anesthetic effect in the positive control group (G) lasted for 8.2 ± 1.79 min. The anesthetic effect in groups H-K treated with graded doses of the extract following ketamine hydrochloride anesthesia was also enhanced in an increasing dose fashion in all the groups but significantly more in groups I, J and K (Fig.2; $P < 0.001$). Those rats in group L that were injected with the leaf extract alone at a dose of (400 mg/kg) were sedated for 8 ± 1.56 min.

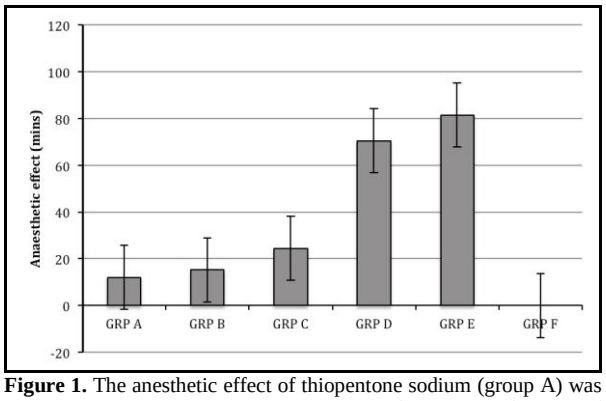

Figure 1. The anesthetic effect of thiopentone sodium (group A) was prolonged by 100, 200, 400, and 800 mg/kg of aqueous leaf extract of *Olea hochstetteri* in groups B-E, respectively. The dose of thiopentone sodium was 30 mg/kg BW administered IP. Group F were administered normal saline only. Each value was expressed as means and standard deviations of 5 rats.

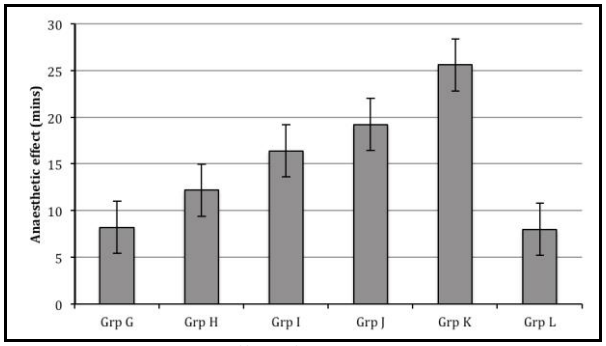

Figure 2. The anesthetic effect of ketamine hydrochloride (group G) was prolonged by 100, 200, 400, and 800 mg/kg of aqueous leaf extract of *Olea hochstetteri* in groups H-K, respectively. The dose of ketamine hydrochloride was 30 mg/kg BW administered IP. Group L were administered normal saline only. Each value was expressed as means and standard deviations of 5 rats.

DISCUSSION

Humans and animals may be exposed to certain principles as ingredients in food and herbal medicinal products, which may interact with anesthetic drugs with potentials either to reduce or increase their anesthetic effects. The intraperitoneal LD_{50} of *O.hochstetteri* has been calculated to be 1280 mg/kg and this suggests that the extract is safe and not toxic [20]. The results of the present study showed that *O.hochstetteri* enhanced the anesthetic effects of thiopentone sodium and ketamine hydrochloride in a dose-dependent fashion.

Olive leaf has been shown to contain iridoid compounds which have vasorelaxant effect [21]. Calcium ion channel-blocking activity of olive leaf extract also has antinociceptic property [9]. The presence of sterols and triterpenes in the *O.hochstetteri* leaf extract may also modulate the anesthetic effect of thiopentone and ketamine because Li Lin *et al* [11] showed that monoterpene alcohols which are found in some plants increased propofol concentration in the blood by inhibiting its metabolism. Increase in the sleeping time of the anesthetic drugs following administration of *O.hochstetteri* leaf extract may support the folkloric claims of olive as being a hypnotic agent. Differences were observed in the two figures with the Fig.2 (ketamine hydrochloride) being a straight-line graph as compared with that of thiopentone sodium and *O.hochstetteri* treatment. This could be due to differences in the bioavailability and transformation of the two anesthetic agents but this remains to be determined.

Other herbs that can prolong anesthetic effect include the Valerian which has the potential to prolong thiopentone- and pentobarbitone-induced sleep [22] by acting on the $GABA_A$ receptor, responsible for sleep induction, and therefore not recommended for use with barbiturates. Kava kava is a herbal anxiolytic used for insomnia and nervousness and contains the α-pyrone as the active principle which has an agonist effect on the γ-aminobutyric acid (GABA)/benzodiazepine receptor [23]. Another herb St John's wort has also been shown to produce sedation and is thought to prolong anesthesia by inhibition of synaptic reuptake of serotonin, noradrenaline, and dopamine [24].

In conclusion, *O.hochstetteri* leaf extract contains principles that prolongs the anesthetic effects of thiopentone sodium and ketamine hydrochloride and may result from alterations in their biotransformation and/or metabolism, which requires additional research. We recommend that medical practitioners and anesthesiologists should evaluate patients on the use of phytotherapy especially when general anesthesia is indicative. Attention should also be given to patients that are vegetarians, as different plants may interact with any form of interventions that may be prescribed.

CONFLICTS OF INTEREST

None to declare

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