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Department of Hygiene, Medical University of Lublin

DOROTA ŻÓŁKOWSKA, ANNA PIKUŁA,
ANDRZEJ BORZĘCKI, MARIA SIEKLUCKA-DZIUBA

Interaction between local anesthetics and centrally acting antihypertensive drugs

Local anesthetics are widely used in alleviating pain concomitant with small surgery procedures and in dentistry. Lidocaine is a local anesthetic and antiarrhythmic agent blocking sodium channels (9). Especially medication in ductal anesthesia after penetrating into systemic circulation can have asignificant influence on the central nervous system and stimulus conduction in the heart (10). Clonidine and reserpine are centrally acting antihypertensive drugs (5).

The aim of this study was to examine an interaction lidocaine (LID), articaine (ART) and mepivacaine (MEP) with some antihypertensive drugs clonidine (CLON) and reserpine (RES) on the pentylenetetrazole induced seizures.

MATERIAL AND METHODS

Animals. The experiments were carried out on female mice weighing 20-25 g housed in standard laboratory conditions. The animals were chosen randomly and assigned to experimental groups of 10 animals.

Seizure activity. Chemical seizures were induced by pentylenetetrazole (Sigma, St. Louis, MO, USA). The animals were observed for 30 min for the occurrence of clonic seizure activity. The measure of seizure susceptibility were clonic seizures, considered as clonus of the whole body, lasting over 3 s, accompanied by the loss of righting reflex. The convulsive potencies of the substances were evaluated in the form of CD_{50} (convulsive doses 50%).

Substances. The following substances were used: local anesthetics – lidocaine (Lignocainum HCl – Polfa-Warsaw, Poland), mepivacaine (Scandonest 3%, Septodont,

France) and articaine (Ultracain D-S/Forte, Hoechst, Germany), antihypertensive drugs – reserpine (Serpasil, Ciba-Geigy, Switzerland) and clonidine (Iporel, Jelfa, Poland). Local anesthetics were applied subcutaneously (s.c.) 10 min before pentylenetetrazole. Clonididine was applied intraperitoneally (i.p.) 2 hours before pentylenetetrazole. Reserpine was applied intraperitoneally (i.p.) 2 and 24 hours before pentylenetetrazole. Calculation of data and statistical analysis: evaluation of the CD_{50} values of pentylenetetrazole were performed with the computer probit analysis based upon the method of Liethfield and Wilcoxon (6).

RESULTS AND DISCUSSION

Local anesthetics work by blocking voltage-gated Na^+ channels (1, 4). They can lead to excitation of central nervous system, anxiety, tremor and seizures (3, 8). Lidocaine has a concentration-dependent effect on seizures (2). Articaine is a well-tolerated and safe and local anesthetic (7). In our study lidocaine (50 mg/kg) and mepivacaine (50 mg/kg) significantly decreased the CD_{50} value of pentylenetetrazole from 80.7 mg/kg to 56.7 mg/kg and from 80.7 mg/kg to 67.9 mg/kg, respectively being ineffective at the dose of 25 mg/kg. Articaine (50 mg/kg) did not influence the CD_{50} value of pentylenetetrazole

Tab.1. The influence of local anesthetics (lidocaine, mepivacaine, articaine) on the pentylenetetrazole induced seizures

Drug	CD_{50} (convulsive doses 50%) mg/kg
PTZ	80.7 [75.4 – 86.4]
PTZ + LID (50 mg/kg)	56.7 [54.7 – 58.7] ***
PTZ + LID (25 mg/kg)	76.3 [71.7 – 81.3]
PTZ	81.5 [74.7 –88.9]
PTZ + MEP (50 mg/kg)	67.9 [62.7 – 73.5] **
PTZ + MEP (25 mg/kg)	85.0 [78.0 –92.5]
PTZ + ART (50 mg/kg)	85.2 [78.4 – 92.7]

*$p<0.01$, **$p<0.001$.

(Tab. 1). Clonidine inhibits release of noradrenaline from neurons and reserpine slightly inhibits collecting of neurotransmiters in neurons (5). Co-administration of local anesthetics with reserpine (0.25 mg/kg 2 hours before the test and 0.5 mg/kg 24 hours before the test – results not shown) did not affect the convulsive activity of pentylenetetrazole. Co-administration of clonidine (0.15 mg/kg 2 hours before the test)

with articaine (50 mg/kg) significantly elevated the CD_{50} value of pentylenetetrazole from 74.0 mg/kg to 91.5 mg/kg. The suppression of sodium channels by local anesthetics would be expected to reduce membrane excitability (10). Co-administration of clonidine (0.15 mg/kg 2 hours before the test) with lidocaine (25 mg/kg) and mepivacaine (25 mg/kg) did not influence the CD_{50} value of pentylenetetrazole. Co-administration of clonidine (0.15 mg/kg 7 days before the test) with local anesthetics did not potentiate convulsive action of pentylenetetrazole (Tab. 2).

Table 2. Influence of co-administration of local anesthetics with antihypertensive drugs (clonidine and reserpine) on the pentylenetetrazole induced seizures

Drug	CD_{50} (convulsive doses 50%) mg/kg
PTZ	74.0 [64.4 – 85.0]
CLON (0.15 mg/kg) + LID	79.7 [69.1 – 85.0]
CLON (0.15 mg/kg) + MEP	76.9 [69.8 – 84.8]
CLON (0.15 mg/kg) + ART	91.5 [81.9 – 102.1] *
CLON (0.075 mg/kg) + ART	85.8 [76.8 – 95.9]
PTZ	78.8 [70.6 – 87.9]
CLON (0.15 mg/kg 7x) + LID	78.9 [74.9 – 83.1]
CLON (0.15 mg/kg 7x) + MEP	79.6 [71.1 – 89.2]
CLON (0.15 mg/kg 7x) + ART	86.8 [80.4 – 93.6]
PTZ	75.5 [66.8 – 85.4]
RES (0.25 mg/kg) + LID	78.8 [70.6 – 87.9]
RES (0.25 mg/kg) + MEP	83.6 [78.0 – 89.5]
RES (0.25 mg/kg) + ART	83.6 [78.0 – 89.5]

*$p<0.05$.

CONCLUSIONS

1. Articaine is the most safe local anesthetic and can be used in epileptic patients.
2. Co-administration of local anesthetics with centrally acting antihypertensive drugs did not influence seizures activity in mice.

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SUMMARY

Local anesthetics are widely used in alleviating pain concomitant with small surgery procedures and in dentistry. Especially medication in ductal anesthesia after penetrating into systemic circulation can have significant influence on the central nervous system and stimulus conduction in the heart. Clonidine and reserpine are centrally acting antihypertensive drugs.

The aim of this study was to examine an interaction of lidocaine, articaine and mepivacaine with some antihypertensive drugs clonidine and reserpine on the pentylenetetrazole induced seizures. In conclusion: articaine is the most safe local anesthetic and can be used in epileptic patients Co-administration of local anesthetics with centrally acting antihypertensive drugs did not influence seizures activity in mice.

Interakcje między środkami miejscowo znieczulającymi i centralnie działającymi lekami hipotensyjnymi

Leki znieczulające miejscowo są szeroko stosowane jako środki znoszące uczucie bólu przy małych zabiegach chirurgicznych i stomatologicznych. Ponadto znajdują zastosowanie jako leki antyarytmiczne. Ich mechanizm działania polega między innymi na zapobieganiu powstawania i przewodzenia impulsów we włóknach nerwowych poprzez blokowanie napięciozależnych kanałów sodowych w błonie komórkowej. Istotne znaczenie w wywoływaniu działań niepożądanych przez leki znieczulające miejscowo ma ich oddziaływanie na czynność ośrodkowego i obwodowego układu nerwowego oraz mięsień sercowy. Celem naszej pracy była ocena interakcji lidokainy, mepiwakainy oraz artykainy z ośrodkowo działającymi lekami hipotensyjnymi klonidyną i rezerpiną w modelu drgawek pentylenotetrazolowych. Lidokaina (50 mg/kg) oraz mepiwakaina (50 mg/kg) w sposób istotny statystycznie obniżały CD_{50} pentylenetetrazolu z 80,7 mg/kg na odpowiednio 56,7 mg/kg i 67,9 mg/kg, nie powodując podobnego efektu w dawce 25 mg/kg. Artykaina (50 mg/kg) nie zmieniała CD_{50} pentylenetetrazolu. Nie zaobserwowano obniżenia CD_{50} pentylenetetrazolu przy jednoczesnym stosowaniu leków znieczulających miejscowo z klonidyną i rezerpiną. Artykaina (50 mg/kg) stosowana łącznie z klonidyną (0,15 mg/kg) istotnie statystycznie podwyższała CD_{50} pentylenetetrazolu. Podsumowując: łączne stosowanie leków znieczulających miejscowo z ośrodkowo działającymi lekami hipotensyjnymi, jak klonidyna i rezerpina, nie powoduje nasilenia drgawek pentylenetetrazolowych. Artykaina wydaje się najbardziej bezpiecznym środkiem znieczulającym miejscowo, stosowanym u pacjentów z padaczką.