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論　文　名	「RENAL EFFECTS OF THE SELECTIVE ALPHA 2-ADRENOCEPTOR AGONIST, MEDETOMIDINE IN DOGS WITH OR WITHOUT REDUCTION IN RENAL MASS（犬の各種腎機能状態におけるα２アドレナリン受容体作動薬、メデトミジンの腎機能への影響）」
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論文要旨

1. Introduction

The effects of anesthesia on renal function are concern for many veterinary anesthetists because the kidney is a highly specialized organ charged with a diverse set of responsibilities, excrete end products of cellular metabolism and maintain the internal environment of the body. The renal blood flow is a product of systemic arterial blood pressure and compliance of renal vasculature, therefore it may be depressed as a consequence of systemic hypotension, renal vasoconstriction or combination of both as may be seen when sedating or anesthetizing an animal. Accordingly, patients with renal disease are at risk of further deterioration of renal function and acute tubular necrosis when subjected to anesthesia and surgery. Medetomidine is one of the almost recently introduced α2-agonist approved for veterinary use and it has been proved to be a very potent highly specific α2-agonist when given alone or when compared to other drugs, since it induces a longer duration of sedation and analgesia. Like other α2-agonists the

drug is known to reveal a variety of side effects and other pharmacological responses due to α2-receptors activation in a variety of nontargeted tissues including the kidney that raise the questions of its safe use in veterinary medicine. The aim of the present study was to clarify renal effects of medetomidine in dogs with normal or abnormal kidney functions to investigate whether medetomidine could be considered a proper agent for sedating animals with renal impairment.

2. Chapter I: Renal effects of medetomidine in isoflurane-anesthetized dogs with special reference to its diuretic action

This study was conducted on sixteen laboratory healthy beagle dogs classified into four groups. Dogs were anesthetized with propofol 6mg/kg IV and anesthesia was maintained with isoflurane. Medetomidine at doses of 20, 40µg/kg IV and 80 µg/kg IM or 1 ml of saline IV was injected. Urine and blood samples were collected before and at 30, 60, 90 and 120 min following injection. Mean arterial blood pressure (MABP), renal blood flow (RBF), glomerular filtration rate (GFR), urine volume (Uv), urine osmolality (Uosm), free water clearance (CH2O), fractional clearance of sodium (FNa), plasma osmolality (Posm), plasma glucose levels and ADH concentrations were measured.

2-1. Diuretic and natriuretic actions of medetomidine:

Uv significantly increased after administration of 20 and 40µg/kg while after 80µg/kg, Uv did not change. Uosm significantly decreased and FNa increased with all doses of medetomidine.

2-2. Effects of medetomidine on MABP, RBF and GFR:

Following medetomidine administration MABP showed an initial increase 5-15 min followed by a long-standing decrease till the end of experiment. The increase in blood pressure was significant when medetomidine was injected IV than when it was

given IM. RBF and GFR significantly increased after administration of 20 and 40μg/kg and decreased after 80μg/kg.

2-3. Effects of medetomidine on plasma glucose levels:

Mean plasma glucose concentrations initially increased then subsequently decreased.

2-4. Effects of medetomidine on Plasma ADH concentrations:

Plasma concentrations of ADH significantly decreased after administration of 20 and 40μg/kg and increased in animals treated with 80μg/kg.

3. Chapter II: The effects of administration of ADH and aldosterone on medetomidine-induced diuresis and natriuresis in isoflurane-anesthetized dogs.

This study was conducted on twelve healthy laboratory beagle dogs classified into 3 groups. Medetomidine, at dose rates of 20μg/kg as a bolus followed by 0.5 μg/kg/min and at 40μg/kg followed by 0.9μg/kg/min or sterile saline (control) was infused along the whole experiment. ADH (100mu/dog) or aldosterone (5μg/kg) was injected at 120 minutes of medetomidine or saline infusion. Urine and blood samples were collected before and at 60, 90, 120,140, 160 and 180 minutes after initiation of saline or medetomidine infusion. Uv, Urine specific gravity (Usp), Uosm, rate of urinary sodium excretion (UNa), Posm, packed cell volume (PCV) and plasma aldosterone concentrations were measured.

3-1. Effects of ADH on the diuretic and natriuretic responses to medetomidine:

Uv markedly decreased following ADH administration that was accompanied by an increase in Usp and Uosm. Posm and PCV decreased and UNa did not change.

3-2. Effects of aldosterone on the diuretic and natriuretic responses to medetomidine:

Uv further increased and Usp and Uosm further decreased after aldosterone injection. Posm and PCV further increased and UNa did not change.

3-3. Effects of medetomidine on Plasma aldosterone concentrations:

Plasma aldosterone did not change after medetomidine administration.

4. Chapter III: Renal effects of medetomidine in isoflurane-anesthetized dogs with reduced renal mass.

Renal effects of medetomidine were investigated in anesthetized twelve laboratory beagle dogs with a reduction in renal mass. Renal mass was reduced by right nepherectomy and infarction of the residual kidney by ligating the medial branch of the left kidney. Three weeks after completion of surgery, medetomidine at doses of 20, 40μg/kg IV or 1 ml of saline IV was injected. MABP, RBF, GFR, Uv, Usp, Uosm, urine PH (UPH), CH2O, FNa, Posm, plasma ADH and plasma aldosterone concentrations were measured.

4-1. Effects of medetomidine on MABP, RBF and GFR:

MABP significantly increased 5 min after medetomidine administration. This increase was followed by subsequent decrease but the values were significantly higher than the control values until 40 min. RBF and GFR significantly increased. Significant differences were not seen between both medetomidine doses from each other.

4-2. Diuretic and natriuretic effects of medetomidine:

Uv significantly increased after medetomidine administration. Usp and Uosm significantly decreased and UPH significantly increased. FNa significantly increased. Significant differences were not seen between both medetomidine doses from each other

4-3. Hormonal effects of medetomidine:

Plasma concentrations of ADH significantly decreased by medetomidine administration and plasma aldosterone levels did not change.

5. Conclusion

· Administration of medetomidine at dose rates of 20 and 40μg/kg increases RBF and GFR and results in profound diuresis up to 2 hours.

· Diuretic effects of medetomidine are the result of suppression of ADH release from the CNS and not due to interference with the hydroosmotic action of ADH on the collecting ducts.

· Compared to aldosterone, ADH appeared to have the most powerful effects in antagonizing the diuretic action of medetomidine while the natriuretic effects appear to involve other mechanisms independent of both hormones.

· Medetomidine at doses of 20 and 40μg/kg increases RBF and GFR and Uv in dogs with reduced renal mass, therefore medetomidine could be safely used for sedating renal patient dogs.

審査結果の要旨

一般に鎮静麻酔薬は全身的に血圧を低下させ、腎血流量を減少し、尿量を減少させることにより、特に腎疾患をもつ患者において腎機能を悪化させることが知られていおり，腎不全動物における麻酔は回避するか，あるいは極めて慎重な管理が必要とされており，より腎臓に保護的に作用する麻酔方法の確立が強く要望されている．一方，特異性の高いα２アドレナリン受容体作動薬であるメデトミジンは、近年、獣医臨床領域で鎮静・鎮痛薬として，また麻酔前投薬として広く用いられているが，他の鎮静・麻酔薬と同様に腎不全では適用外とされてきている．しかし，同薬剤は他のα２アドレナリン受容体作動薬と同様に利尿効果を持つ可能性が指摘され，麻酔中の腎保護作用を有する可能性があるが，犬および猫などの小動物での作用効果，およびその効果を利用した小動物臨床への応用可能性などについてはほとんど検討されていない.

本論文では，腎不全罹患犬の安全な麻酔法への本薬剤の応用可能性を検討するために，健常犬および実験的に作成した腎不全犬を用いて、イソフルラン吸入麻酔下におけるメデトミジンの腎機能への影響とその機序について調べた。

成果は以下のように要約される。

第 1 章では, イソフルラン吸入麻酔下での健常犬におけるメデトミジンの薬理作用を明らかとするため、臨床で使用される用量（20、40μg/ml）および高用量（80μg/ml）のメデトミジンを健常犬に投与し，その作用効果を検討した。臨床用量のメデトミジン投与では、腎血流量および糸球体濾過率が増加し、その結果、尿量が増加した。メデトミジン投与後、尿浸透圧は有意に減少し、尿へのナトリウム排泄は増加した。さらに、血中抗利尿ホルモン（ADH）濃度が低下する事が明らかとなった。一方で高用量のメデトミジン投与では、尿浸透圧および尿へのナトリウム排泄は有意に増加し、腎血流量および糸球体濾過率は減少し，尿量は減少した。また、血中 ADH 濃度はわずかに増加する事が明らかとなった。これらの結果から、健常犬でのメデトミジンの薬理作用の発現および臨床用量と高用量における作用の差異は、メデトミジンが中枢において ADH の分泌調節に関与をした結果であることが示唆された。

第 2 章では、メデトミジンの腎機能に対する作用をより詳細に検討するため、メデトミジン投与後の抗利尿ホルモン（バソプレシン）および尿中へのナトリウム排泄を調節する作用を持つ鉱質コルチコイド（アルドステロン）添加試験を実施した。その結果，バソプレシンを投与すると、顕著な尿量の増加の抑制と尿浸透圧および尿比重の増加を誘導した。しかし、アルドステロン投与では、メデトミジンの利尿効果やナトリウム尿排泄効果に変化は生じなかった。これらの結果から、メデトミジンによる利尿効果は抗利尿ホルモンの腎臓における作用を抑制しているのではなく、中枢性に分泌を低下させている事が一因であると考えられた。

第 3 章では、腎機能低下時におけるメデトミジンの作用を明らかとするため、腎臓の部分摘出により作成した腎不全モデル犬を用いて検討した。その結果，健常犬と同様にメデト

ミジン投与により、腎血流量および糸球体濾過率の増加と尿量の増加が認められ，また、血中の抗利尿ホルモン濃度はメデトミジン投与により有意に減少した。一般的に腎機能低下症例における麻酔はその危険度が上昇する事が知られているが、これらの結果から、メデトミジンを麻酔に応用する事でより安全に麻酔を実施出来うる可能性が示唆された。

審査委員会の所見

以上のような試験から、本論文では、健常犬ならびに腎不全モデル犬においてメデトミジンの腎機能に対する作用を明らかとし、その結果、メデトミジンは腎血流量および ADH 分泌抑制を介して尿量を増加させる事によって腎機能の維持に寄与し、比較的安全な鎮静薬であることを示し，腎不全動物での有用な麻酔法となりうる可能性が大きいことを確定した.

本論文の成果は獣医臨床学に大きく貢献するものである。よって、最終試験の結果と併せて，博士（獣医学）の学位を授与することを適当と認める。