Psychopharmacology: an approach to medication on behavioural cases

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What is a psychotropic drug?

What is a psychotropic drug?

- Substance able to induce behavioural changes
- Actions:
  - Presynaptically (afecting the action potential)
  - Synthesis, metabolism, storage, release, reupatake or degradation of one or more neurotransmitters
  - Postsynaptically (binding to or modifying receptors)

... To have success in our behavioural modification protocol...

... MANY TIMES WE HAVE TO PRESCRIBE!!!

Behind the operant conditioning ...

... it is the important role of the cognitive and relaxation therapy. And to achieve that with success in dogs and cats treatment, medication could be a need!

3 groups of Neurotransmitters we want to work with:

- Amino acids (gama-aminobutyric acid (GABA), glutamate and glycine)
- Amines (acetylcoline (Ach) and monoamines (dopamine, serotonine, norepinephrine)
- Peptides (cholecystokinin (CKK), substance P and neuropeptide Y)

Important action and side effects on behaviour modification:

- Gama-aminobutyric acid (GABA),
- Acetylcoline (Ach),
- Dopamine,
- Serotonine,
- Norepinephrine.

The world of suplements

Nutraceutics

- After 2006 appeared in the market other molecules for possible use:
  - Nutraceutics
  - Needs critical read
- Several products:
  - Anxitante
  - Zylkene
  - Kalmaid
  - Calm – Royal Canin

Action mode:

- Fixing to a sub-structure of GABA-A receptors
- Structural afinity to BZD receptors

Neurotransmitters' a.a. Precursors

- Tryptophan and tyrosin are precursors from serotonine and dopamine
- This precusors a.a. Can affect the incidence of aggression, auto-mutilation and pathology resistence

Other diet supplements – the main goal

- Keep or improve the structure of neurons' membranes
- Neuroprotection
- Protection from oxidative stress
- Improve cognition

PUFA – poliunsaturated fatty acids

HERBS

St. John's Wort

Psychopharmacology drugs applications

PSYCHOPHARMACOLOGY

- **Long action Anxyolitics…**
  - … continuous and/or chronic use
  - … specific to serotonine
  - … action over several neurotransmitters

- Tricyclics Antidepressants (Clomipramine)
- Selective Serotonin Reuptake Inhibitors (**SSRI**) (Fluoxetine)
- BZD, TZD, Dexmedetomidine, Gabapentine, Pregabaline, Tasipimidine

- Secondary effects: decrease or increase in activity (due Dopamine and serotonine levels); Desinhibition; paradoxyc effect, anorexia; BZD and learning….
- Requires ongoing monitoring and special attention at the weaning (stress and anxiety signs)

Aitäh!

Let's speak about serotonine, the welfare and harmony neurotransmitter

SEROTONINE

- Monoamine
- Very spread
- Regulate several behaviours

SEROTONINERGIC SYNAPSIS

5-HT Agonists- BUSPIRONE

- Its action is in pre-synapsis, to increase the quantity of liberated serotonine
- Effects due to increase of serenity because the animals is less anxious; increase the "asservitivy" but doesn't increase agonistic behaviours (as reactivity)

Buspirone

- Less sedation then BZD
- Takes 1-3 weeks to start its action
- Gradual weaning

- Indicated to general anxiety disorders (as BZD)
- It is not effective on panic problems as it has no immediate effect
- Generally used in:
  - Cat's secondary to stress marking
  - Agressivity interespecific due to fear

Dosage

- Dog (very rarelly used!)
  - 1mg/kg q8-12h

- Cats
  - 0,5-1mg/kg q8-12h

Tricyclic antidepressants (TCAs)
Serotonine Reuptake Inhibitor

- Clomipramine
- Amitryptiline
- Nortryptiline
- Imipramine
- Desipramine
- …

CLOMIPRAMINE
Tricyclic antidepressant

Action:

- Reuptake inhibitor of both serotonine and noradrenaline
- Muscarinic, histaminic, alfa-adrenergic effects
  Responsables for the secondary effects but also some of desired therapeutical effects
- Action in nociceptive fibers: action on pain!

Indications

- Permanent Anxiety
- Learning and cognitive problems
- Reactive sociopathy
- Separation Anxiety
- Secondary Hyperattachment
- **TOC**
- Interstitial Cystitis (*Amitryptiline – marking in cats*)
- Neuropathic Pain

Contra-indicated

- Glaucoma
- Seizures
- High risk of confusion in the senior dog
- Risk of desinhibition in low doses

Side effects

- Urinary: stranguria (anticolinergic effect)
- Digestive: constipation (anticolinergic effect) and nausea
- Sedation (antiH1 effect) – mainly in the beggining (start with low doses)
- Weight gain (antiH1 effect)
- Tongue movements due dry mouth (muscarinic effect)
- Desinhibition in low doses
- Heart: Arrithmic frequency (ECG), taquicardia, hipotension
- Potentiate thyroid changes
- Sexual disfunction

Side undesired effects – STOP TX

Dosage

- 1 to 4mg/kg
- Progressive need to wean the dose when the treatment take more than one month

Avoid simultaneous use with barbiturics, SSRI, opioids
Never use with a iMAO
Cimetidine – decrease the antidepressants effect and increase the possibility of toxicity
Not use with AMITRAZ (it is an iMAO)

SELECTIVE SEROTONINE REUPTAKE INHIBITOR (SSRIs)

ACTION MODE

ACTION:

- Modification of neurotransmitter concentration
- Adaption of the synapsis (down-regulation effect)
- The drug effect should only be assessed after a minimum period of 15 days after starting the treatment.

Indications:

- In a low dose has an antidepressant and anxyolitic action
- In high dose is indicated to:
  - Agitation
  - Impulsivity
  - "Aggression"

DOSE

- 0,5-4mg/Kg/SID po
- Attention with: anorexia, epilepsy (**??**), reactivity (in lower doses!!!)

Side effects

- Nausea
- Anorexia
- Letargy
- Trembling
- Excitation (mainly in low doses)
- Insomnia

Serotonin antagonist and reuptake inhibitors (SARIs)

- antagonizing serotonin receptors such as 5-HT_{2A}
- inhibiting the reuptake of serotonin, norepinephrine, and/or dopamine.

Trazodone

- Not specific: affects receptors 5-HT2A, 5-HTC2C, alfa2adrenoreceptors and other monoamine receptors but has a low anticolinergic effect
- Can have a strong sedative effect (great support for clinical procedures)
- 1,7mg/kg/d-7,25mg/kg/d po

- Supportive treatment in cases of fear, separation related problems together with TCAs ou SSRI
- Side effects:
  - GI
  - Priapism
  - Sedation

2. Medication that affects NE/NA

Let's start talking about norepinephrine/noradrenaline, the neurotransmitter of fear and stress

NA/NE

Catecolamine

precursor: tyrosine

- Neurotransmitter
  - Produced by the *locus coeruleus* and post-ganglionar fibers
- Hormone
  - Produced by the adrenal glands

Role of NA/NE

In the brain:
locus coeruleus

Central role (NA)

- Stimuli filter
- Attention focus and focalized mental activity
- Thinking discrimination
- Mood regulation
- Regulation of energy and fatigue
- Increase memory (specially in negative events!!)

Role of NA/NE

Periferically:
Fear response
(with HHA axis activation and hormonal release)

NA/NE

alfa and beta receptors

NA/NE receptors

- Alfa receptors
  - Contraction of muscular fibers: heart, vascular, digestive, genital and urinary system
- Beta receptors
  - Relaxation of muscular fibers

Alfa Effect happens in low doses, while the beta Effect in high doses

Periferic signs of fear (NA)

- Trembling
- Sweating
- Dry mouth or hypersialia
- Urination/Defecation
- Vagal Shock sometimes with syncope

Nor-adrenergic symptoms (central)

- Decreased NA (deficit)
  - Attention changes
  - Concentration difficulties and cognition
  - Fatigue, energy lack

Nor-adrenergic symptoms (central)

- Excess of NA
  - Neurovegetative Symptoms
    - Tachycardia, tachypnea, mydriasis, sweating, tremors
  - Emotional urination
  - Release of the contents of the anal sacs
  - Insomnia, hyposomnia
  - Hyperstesia, hypervigilance
  - Uncontrolled aggressiveness
  - Avoidance
  - Displacement activities
  - Epileptiform seizures and syncope

NA/NE psychotropic medications

NA/NE psychotropic medications

- Reuptake inhibitors
  - Clomipramine
- Tranmission inibhitors
  - Beta-blockers: propanolol
- Alpha-2-agonists:
  - Clonidine
  - Tasipimidine
  - Dexmedetomidine

Propanolol

- Action mode
  - Block the beta post-sinaptic receptors: inhibit the NA/NE trasmission
  - Effects: hypotension, negative chronotropic, hypoglycemic, decrease of thyroid releases

Contraindications and side effects

- Contraindications
  - Diabetes
  - Hypothiroidism
  - Cardiac disease in the senior dog
  - Anesthesia
- Secondary effects
  - Sedation in high doses

Tasipimidine, an alpha-2A agonist: a new active substance in veterinary medicine

- Fear/anxiety, as well as learning and memory, are mediated in the locus coeruleus (neurons are rich in alpha-2 receptors)
- Stressors increases the release of noradrenaline from the locus coeruleus
- Tasipimidine binds to pre-synaptic alpha-2A receptors reducing release of noradrenaline

⇨ **Leads to a reduction of anxiety**

Sileo

Dexmedetomidine – Mode of action

- **The active substance**: Dexmedetomidine, a highly potent and selective alpha - 2 adrenoceptor agonist
- **The anxiolytic effect:** Mediated through the locus coeruleus in the brainstem, with noradrenaline (NA) as the main neurotransmitter
- **How:** Dexmedetomidine binds with the pre-synaptic alpha - 2 adrenergic receptors in the locus coeruleus, preventing or reducing the release of noradrenaline. Lower levels of norepinephrine in turn reduce the physiological and behavioural manifestation of stress, fear and anxiety

Orion Pharma

3. Medication that affects GABA

- Inhibitor aminoacid

Precursor:
Glutamate

"Gabaergic" Pathways

- Spread almost in all brain structures
- Several authors say that 30 to 50% of inhibiting neurons are "gabaergics"

BENZODIAZEPINES

- Historical modulators
- GABA potentiators
- Very common use in human medicine
  - But also in veterinary field

Benzodiazepines

- Diazepam (Valium)
- Clorazepato
- Clordiazepoxide
- Alprazolam (Xanax)
- Oxazepam
- Lorazepam (Lorenin)

BENZODIAZEPINES

- Apart from its anxyolitic effect:
  - Have a sedative effect
  - But also can cause amnesia and desinhibition

Benzodiazepines and hepatotoxicity

- Important role of N.desmetildiazepam
  - oxazepam and alprazolam do not follow this path!
- Feline metabolism?
- **What is the internacional experience?**

Weaning in continuous treatments?

YES!!

Habituation and dependence effect in humans...

What else affects the GABA?

Gabapentine

- Similar structure to GABA
- Does not interact as percursor, agonist or antagonista from GABA
- Increase GABA intracelular and in the brain
- Modulation of Na+ channels and increase the blood concentration of serotonin
- It is not metabolized – precaution with CKD.

Use in humans

- Epilepsy (in partial seizures)
- Neuropathic pain
- Locomotion Desequilíbrios locomotores
- Headackes
- Ansiety – panic attacks, social fobia
- Bipolar disease

Carefull with dependence and weaning

Dose and side effects

- Side effects:
  - Few as there are no active metabolits (no hepatic metabolism, that´s why it requires attention with kidneys that will receive the entire drug)
- Dose:
  - T ½ = 6-8 in humans (in dogs is similar, but a bit faster)
  - Dose 1-3 times per day – 10-30mg/kg po q.8-24h
  - Starting with a maximum dose of 200mg1-3x/dia depending in other medications and effects

Bonqat

ORION PHARMA ANIMAL HEALTH

PREGABALIN: NEW ACTIVE SUBSTANCE IN VETERINARY MEDICINE

Mechanism of action in the central nervous system:

- Binds to presynaptic neurons at the alpha2-delta subunit of voltage-gated calcium channels reducing calcium influx to the cell
- Decreased calcium influx **reduces excessive release of several excitatory neurotransmitters** (glutamate and monoamine neurotransmitters)

⇨ **Decreases the level of anxiety**

Bonqat

HOW DOES PREGABALIN/BONQAT® DIFFER FROM GABAPENTIN?

- **Mode of action** is exactly the same → so are the expected **side effects** (tiredness and incoordination)
  - Also the **onset of action** is about the same
- Pregabalin could be seen as the 'next generation' gabapentin as it is **more potent** and has **better PK properties** in cats
  - Half-life of pregabalin is longer than that of gabapentin (14 h vs. 4 h), so the effect has a **longer duration**
- In humans, it has been shown that **pregabalin is absorbed more quickly** and its **absorption is linear**, whereas gabapentin's absorption becomes saturated with increasing dosage, i.e. the bioavailability decreases

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Bonqat

HOW DOES PREGABALIN/BONQAT® DIFFER FROM GABAPENTIN?

- Bonqat® provides **more accurate, rigorously studied dosing** (5 mg/kg) compared to gabapentin (50–150 mg/cat)
- Bonqat® is **easier to give**: it has a very small dosing volume (0.1 ml/kg), acceptable flavour, and in our clinical field study, cat owners found it very easy (48.1%) or to easy (30.6%) to give
  - Giving pills to cats is notoriously difficult (gabapentin mostly available as pills)

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Medication that affects dopamine

Talking about dopamine, that is the neurotransmitter of pleasure and desire

SYNTHESIS

Precursor: Tyrosine

DEGRADATION

RECEPTORS

DOPAMINERGIC PATHWAY

ADICTION

- Normal individual/adicted individual

MESOCORTICAL PATHWAY

- Concentration, memory
- Depression

ATTENTION
MAINTENANCE LEARNING
COGNITION

Selegiline

- Action mode:
  - Regulator of DOPAMINERGIC and noradrenergic functions
  - **Selective Inhibitor of Mono Amino-oxidase (iMAO-B)**

MAO Enzime

MAO Inhibitor

Selegiline

- **Other action modes:**
  - Protect cells from oxidative stress and toxic effect of free radicals
  - Inhibition of several neurotoxines (protect the dopaminergic neurones)
  - Selective action in nigrostriatal pathway (Parkinson)

Used for Cognitive Dysfunction

- Learning (mesocortical pathway)
- Neuroprotector action (against neurotoxines, free radicals)
- Sleeping cycles

- Improve short term memory – motivation and antecipation
- Reduction of clinical signs related with CDS – attention, cognition,
- Increase longevity

It is recommended the administration in the morning, specially when there are changes in sleeping cycles.

- If there is therapeutical success than is for the rest of the animals life;
- But it is always required to treat at least during 8 weeks to see if the drug has efficacy or not

Dose, side effects

- Dog: 0,5 mg/kg daily in the morning (can be duplicated on the senior dog) – Karen Overall says 1mg/kg po q24h
- Cat: 0,25-0,5mg/kg po q 24h (Karen Overall)
- It cannot be used in pregnant or lactating females

Other drugs interactions:

- It cannot be associated with other psychotropic drugs (namely SRI)
- ! Amitraz

Dopamine modulators

- Selegiline
- The neuroleptics
  - **Acepromazine**
  - Haldol
  - Azaperone
  - Levopromazine
  - Pipamperone
  - Risperidona

ACEPROMAZINE

Action:

- Sedative neuroleptic
- Block receptors D2 post synapsis
- Block receptors H1, NA, M

Acepromazine

- Indications
  - Anestetic pre-medication
  - Trips: as sedative and anti-emetic
  - Before euthanasia

Acepromazine

Sedation

Drastic decrease of motor activity (not able to respond.... Can be in fear, but have no way to manifest it!

Please do not use acepromazine – a dopamine antagonist - as a behavioral medication, particularly for anxiety and storm / noise phobias!!

(Karen Overall)

QUICK QUIZ

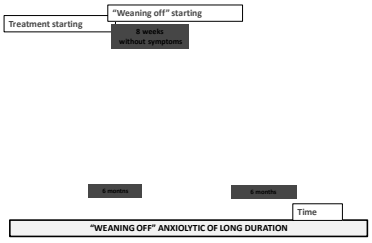
SHALL I DO A DRUG WEANING OR CAN I STOP IMMEDIATELY?

Quick answer

- Some literatures says that medication can be abruptly stopped because they have a long half-time live of its intermediate metabolits
- Nevertheless, weaning allows to identify the minimum effective dose and can prevent from discontinuation syndrome

Discontinuation Syndrome

- May occur with prolonged treatment
- **Can be avoided with proper weaning of medication**
- Signs:
  - Agitation, lethargy, depression, and profound changes in behavior



Are there animals that require medication for ever?

Polymorphism in metabolic capacities (individual reactions)

Understanding this fact will help to choose a drug to a certain traget population

This aspect of the individual metabolism affects the probablity of side effects as the **Serotoninergic Syndrom** and the **Discontinuation Syndrom**

Serotonergic Syndrome

- Excessive serotonergic activity at the central nervous system and/or peripherial – this is a real emergency that, when there, can kill the patient without treatment
- It can be acidental, iatrogenic or due metabolic particularities
- The risk can be higher in small breeds as the adequate dosage can be more difficult to handle
- Non specific signs, including:
  - Changes in the mental state – desorientation, confusion
  - Autonomic Changes – náusea, vomits, diarrhea, fever
  - Neurologic Changes – tremores, tremors, muscle stiffness, incoordination, hyperreflexia, seizures

POLYPHARMACOLOGY

Why to combine drugs?

- Costs
- Receptors specificity
- Animal's metabolism
- Potential side effects when using a higer dose of only one drug
- Multiple behavioural problems that are co-morbid
- Co-morbilid behavioural and other physical/physiological diseases

General rules to combine drugs

- CAN combine meds in same and, or related class – eg TCAs and SSRIs ISRS – in lower dose. The combination decrease the side effects
- CANNOT combine meds that have potential to affect one part of metabolic pathway that could have later multiplicative effects and that carries side effects (eg. Cannot mix TCAs or SSRIs with MAO-i)... The main risk is serotonin syndrome

Possible used combinations...

- Meds that act in different ways at standard dosage, but watch for enhanced ide effects if they share side effects :
  - Any TCA plus any BZD
  - Any SSRI plus any BZD
  - Common Combos:
    - Amitriptilyne or Clomipramine with BZD (SA)
    - Clomipramine+alprazolam or Fluoxetine+alprazolam (AS or CB + panic)
    - TCA or SSRIs daily + BZD in SOS (any anxiety disorder + anxiety at vet's)

Complement to Rules

- CAUTION and decrease dose if end product can be the same
  - For example, buspirone, a partial 5-HT 1A agonist can be given with TCAs and SSRIs, but very carefully as both increase serotonin level
  - Serotonin Syndrome!

Changes of medication

- In the same class:
  - TCA to a SSRI: direct
  - SSRI to a TCA: depends on the plamastic half-life
- To another class:
  - « wash out » period:
    - MAOi->fluoxetine->15 days
    - Fluoxetine->MAOi->3 weeks

Can we combine TCA or SSRI with phenobarbital or other epilepsy medication?

Yes, if the animal NEEDS both….

But phenobarbital is not a behavioural medication. One side effect of all these medications is sedation. If the cliente presents sedation, the pharmacology combination can put them in risk. Barbiturics affect the GABA-A receptors, leading to sedation.

Apart from this fact, a patient that is under anxiolytic medication will need less anti-convulsion medication as they are less anxious. This is a real benefit from polypharmacy!

Shall we stop behavioural medication if it is required an anesthesia?

- No – NO!, do not stop behavioural medication. Select a pre-anesthetic agente that minimize the potential worries (example, avoid alfa-agonists with TCAs).

Close to conclusions

SOME FINAL IDEAS…

Complimentary exams

►BLOOK CHECK-UP TOGETHER WITH A GOOD PHYSICAL EXAMINATION!!!

NEVER forget the importance of combining medication with behavioural modification!

Medication affects the same neurochemical pathway that involve learning and, for that reason, can speed up the behavioural modification of the desired behaviour

Know the client

- Make sure that client understood everything...
- Client is going to buy medication and accomplish the rules?
- Does client have history of drug abuse or dependency?
- Does the client have fear... of the dog or losing him?

Information to owners

- Reason to prescribe medication
- Advantages
- Duration
- Time until there are possible efficacy
- Risks (side effects)

- *Give a phone number for emergencies during the drug treatment!*

Carpe diem!

The use of behavioural medication can create an effective treatment program, scientifically based, and that respect with humane care the needs of everyone's needs.