ANTI-ALLODYNIC EFFECTS OF ABOBOTULINUMTOXIN A (DYSPORT) IN A RAT MODEL OF MRMT-1-INDUCED BONE CANCER PAIN

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ANTI-ALLODYNIC EFFECTS OF ABOBOTULINUMTOXIN A (DYSPORT) IN A RAT MODEL OF MRMT-1-INDUCED BONE CANCER PAIN

Maffre V.[a], Favre-Guilmard C.[b], Kalinichev M.[b], Darbaky Y.[a] and Diop L.[a].

[a]ANS Biotech, Biopôle Clermont Limagne, Site de Riom La Varenne, Riom, France

[b] Ipsen Innovation, Les Ulis, France

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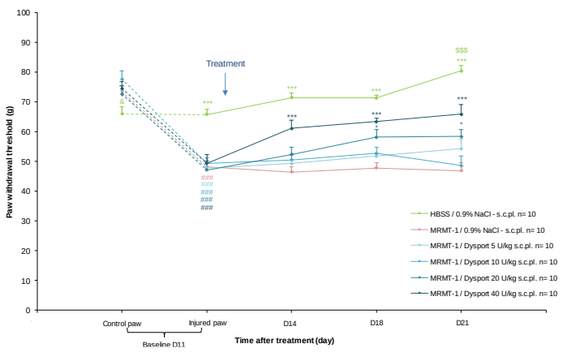
Introduction

A significant proportion of patients with advanced breast, prostate or lung cancer develop skeletal metastasis and suffer from bone cancer pain. The MRMT-1 mammary carcinoma model of bone cancer in rats mimics aspects of the clinical pathogenesis and symptoms, including chronic pain and can be used for evaluation of the efficacy of novel analgesic medication (Medhurst et al. 2002). There is growing clinical and preclinical evidences that in addition to well-characterized muscle-relaxant properties, abobotulinumtoxin A (Dysport) can reduce different types of pain. The objective of this study was to assess the antiallodynic effect of intra-plantar administrations of Dysport in the model of MRMT-1-induced bone cancer pain in rats.

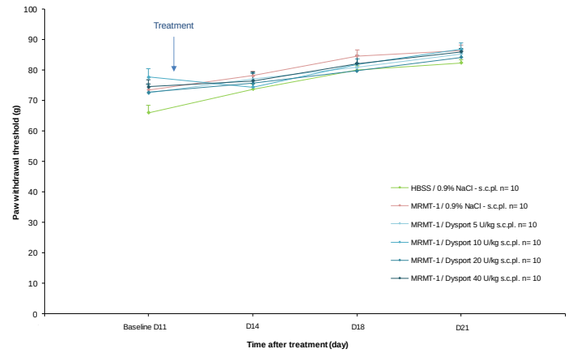
Materials and Methods

Adult male Sprague-Dawley rats were anesthetized before receiving inoculation of 3.10^4 MRMT-1 mammary carcinoma cells into the medullary cavity of the tibial bone or receiving a sham-operation. On day 11 after cancer cell inoculation, animals (n=10/group) received an intraplantar administration of aboBoNT/A (5, 10, 20, 40 U/kg, s.c.pl.) or vehicle (saline). Tactile sensitivity of both hindpaws was measured on day 11 before aboBoNT/A treatment (Baseline) and on days 14, 18 and 21 post inoculation corresponding to days 3, 7 and 10 post aboBoNT/A injection using the electronic Von Frey test. Morphine HCl 3mg/kg s.c. was used as positive reference.

Antiallodynic effects of a single intraplantar administration of aboBoNT/A (Dysport) (D_{11}) in a rat model of MRMT-1-induced bone cancer pain



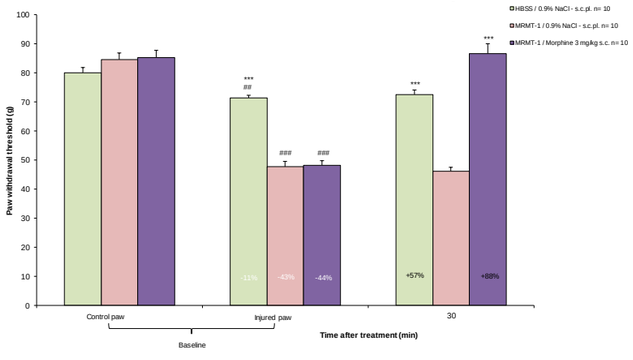
Ipsilateral paw



Contralateral paw

Results are expressed as mean ± s.e.m. ###: p<0.001 as compared to the control paw of the corresponding group, Bonferroni's test after significant two-way ANOVA. *; ***: p<0.05 and 0.001, respectively, as compared to the vehicle-treated group, Bonferroni's test after significant two-way repeated measures ANOVA. $$$: p<0.001 as compared to D_{11} of the corresponding group, Bonferroni's test after significant two-way repeated measures ANOVA. &: p<0.05 as compared to the Dysport 10 U/kg-treated group, Bonferroni's test after significant two-way ANOVA.

Antiallodynic effects of a single subcutaneous administration of Morphine (D_{18}) in a rat model of MRMT-1-induced bone cancer pain



Results are expressed as mean ± s.e.m. Percentage are expressed as decrease or increase as compared to the vehicle-treated group in black and as decrease as compared to the corresponding control paw. ##, ###: p<0.01 and 0.001, respectively, as compared to the control paw of the corresponding group, Bonferroni's test after significant two-way ANOVA. ***: p< 0.001, as compared to the vehicle-treated group, Bonferroni's test after significant two-way repeated measures ANOVA.

Effects of a single local administration of aboBoNT/A (Dysport) (D_{11}) in a rat model of MRMT-1-induced bone cancer pain on body weight

Body Weight (g) mean ± s.e.m.

Groups	D11	D14	D18	D21
HBSS / Vehicle	310 ± 5	341 ± 5	366 ± 8	392 ± 5
MRMT-1 / Vehicle	305 ± 6	325 ± 7	354 ± 8	373 ± 7
MRMT-1 / Dysport 5 U/kg	301 ± 7	328 ± 6	358 ± 5	377 ± 6
MRMT-1 / Dysport 10 U/kg	313 ± 7	336 ± 8	367 ± 8	385 ± 8
MRMT-1 / Dysport 20 U/kg	309 ± 9	332 ± 9	359 ± 9	377 ± 9
MRMT-1 / Dysport 40 U/kg	320 ± 9	344 ± 10	369 ± 10	383 ± 10
MRMT-1 / Morphine 3 mg/kg	302 ± 8	327 ± 9	355 ± 11	375 ± 12

Results

MRMT-1 cancer cells induced, from 11 days to 21 days after inoculation into the medullary cavity of the tibia, a reduced and stable paw withdrawal threshold in the vehicle-treated group. A single intraplantar administration of aboBoNT/A (5, 10, 20 and 40 U/kg) produced, in a dose and time related manner, an anti-allodynic effect on MRMT-1-induced tactile hypersensitivity. Maximum effect was observed with the highest dose of 40 U/kg (32% to 40%, p<0.001) while the lowest doses of 5 and 10 U/kg did not induce any significant effect.

The positive reference, Morphine HCl 3mg/kg s.c., induced a significant analgesic effect by 88%, 30 min after administration.

Contralateral paw withdrawal thresholds and body weights were not impacted by Dysport local injection.

AboBoNT/A did not impact the magnitude of bone damage induced by the tumor. (data not shown).

Conclusion

AboBoNT/A reduces mechanical allodynia induced by MRMT-1 cells in a bone cancer pain model in rats. These results suggest a possible effective and long-lasting reduction in chronic pain associated with metastatic bone cancer in humans.

Study Sponsored by Ipsen

Disclosures:

MK, CF-G: Employee of Ipsen

VM, YD, LD: Employee of ANS Biotech, a biotechnology company who received financial support from Ipsen to work on this study

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CONTACTS

> Dr. Yassine **DARBAKY**
Chief Business Officer
yassine.darbaky@ans-biotech.com
+33 (0)9 70 75 85 02

> Julie **CHAMALET**
Business Development Assistant
julie.chamalet@ans-biotech.com
+33 (0)9 70 75 85 02

www.ans-biotech.com